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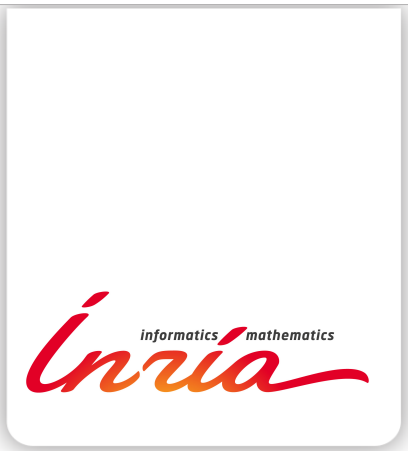

Aedes, *Wolbachia* and Dengue

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Abstract: We present a model of infection by *Wolbachia* of an *Aedes aegypti* population. This model is designed to take into account both the biology of this infection and any available field. The objective is to use this model for predicting the sustainable introduction of this bacteria. We provide a complete mathematical analysis of the model proposed and give the basic reproduction ratio $\mathcal{R}_0$ for *Wolbachia* . We observe a bistability phenomenon. Two equilibria are asymptotically stable : an equilibrium where all the population is uninfected and an equilibria where all the population is infected. A third unstable equilibrium exists. We are in a backward bifurcation situation. The bistable situations occurs with natural biological values for the parameters. Our model is an example of an epidemiological model with only vertical transmission.
This infection model is then coupled with a classical dengue model. We prove that for the complete model the equilibrium with *Wolbachia* for the mosquitoes and without dengue for the human is asymptotically stable for sensible values of the parameters. We prove that, if a sufficiently large population of *Wolbachia* infected mosquitoes is introduced, dengue will disappear.
We use the data of a real trial of releases of infected mosquitoes in Cairns (Australia) to calibrate our model. The calibrated model behaves remarkably well vis à vis the observed field. Then we use then the calibrated model to simulate different scenarios of appearance of dengue. We assume a worst case scenarios of dengue epidemics development and take the large $\mathcal{R}_0$ estimation available in the literature which seems to be 24. The simulations confirm our findings, that a dengue epidemics will not occur if *Wolbachia* infections is sufficiently prevalent in the populations. This suggests that the introduction of *Wolbachia* can become an effective control tool for dengue.

Key-words: Mathematical epidemiology, Dengue, Wolbachia, Aedes, dynamical systems, stability, ODE.

Aedes, *Wolbachia* and Dengue

Résumé : Pas de résumé

Mots-clés : Pas de motclef

1 Introduction

Wolbachia pipientis is a maternally inherited endosymbiotic bacteria found in the majority of arthropods. It is receiving increasing attention due to its potential as a biological control strategy against dengue fever and other vector borne diseases.

Dengue fever is a viral disease transmitted between humans by the bite of infected mosquitos of the species *Aedes aegypti*.

Wolbachia is not a natural parasite of *Aedes aegypti* but the successful introduction of a life-shortening strain of *Wolbachia* into the dengue vector has created a strain with significantly lower vectorial capacity than the wildtype [12, 29, 33, 37, 62, 72, 79]. *Wolbachia* infection reduces the mosquito adult mean life span, as well as interferes with its susceptibility to the dengue viruses [7, 8, 29, 40, 56, 57, 60, 72, 76] The widespread success of *Wolbachia* among arthropods is attributed to its capacity to manipulate host reproduction by inducing cytoplasmic incompatibility (CI), femininization, and other effects, that eventually compensate the high fitness costs of infection. In *Aedes aegypti*, the main mechanism seems to be CI, which causes a reduction in the egg hatch rate of *Wolbachia*-free females that mate with *Wolbachia* infected males. Therefore, uninfected females are at disadvantage compared to infected ones and the prevalence of infection in the population tends to increase by positive frequency-dependent selection [32]. Frequency-dependent selection induces a bistable dynamics where the benefit of CI outweighs the infection costs only when prevalence is high, and most uninfected females mate with infected males. This may be the reason behind the observation that *Wolbachia* prevalence among natural hosts follows a 'most-or-few' pattern with some species carrying a very high load and some with very low [80].

The unique biology of Wolbachia has attracted a growing number of researchers interested in questions ranging from the evolutionary implications of infection through to the use of this agent for pest and disease control : a public web site has been funded by the National Science Foundation of Australia (`http://www.wolbachia.sols.uq.edu.au/about.cfm`), and a research in in pubmeb (`http://www.ncbi.nlm.nih.gov/pubmed`) typing *Wolbachia* gives 1315 results.

Several models have been proposed to investigate the key factors modulating the success of this strategy. These models have suggested that life-shortening strains could be successfully introduced locally but would be unlikely to generate travelling waves to the vicinity [5]. In [25] a continuous model is considered, to investigate the possibility for *Wolbachia* to invade a general population of hosts. Two dimensional continuous models are studied in [45]. The reference [12] develops discrete models to predict the severity of adult life-shortening and in turn are used to estimate the impact on the transmission of dengue virus. The reduction of efficiency in the transmission is not taken into account, since this hypothesis has appeared since 2009. Reference [15] proposes a continuous-discrete model to predict invasion and establishment in a population. A discrete model for establishment in a host population is studied in [22]. The authors of [32, 33] use integral delay-equation model and two stage population structure (juvenile/adult) to represent the dynamic of spread in a host population. Leslie matrix discrete model are used in [62]. Finally, in [64], reaction-diffusion and integro-difference equation models are used to model the spatio-temporal spread of *Wolbachia* in *Drosophila simulans*. The reference [71] considers discrete generations models. The preceding models address the issue of establishing *Wolbachia* in a general population. But these models are not designed for *Aedes aegypti* and does not incorporated data specific to mosquitoes.

A notable exception is [42] where a continuous model for simultaneously studying the introduction of *Wolbachia* into an *Aedes aegypti* population and its effect on dengue infection. The total system is 8 dimensional.

In this paper we propose a compartmental population dynamic models for the spread of *Wolbachia* in a population of *Aedes aegypti*, the major vector for the dengue infection. The issue is to

propose a realistic model to predict the sustainable establishment of *Wolbachia*. Our model will be tested on real releases conducted in Cairn (Australia) [40]. We completely analyze the stability behavior of this model. Then we connect this model with a transmission model of dengue. The main characteristics of the population dynamics given by the model are

- A basic offspring number must be greater than 1, to ensure the settlement of the mosquito population of . An equilibrium, representing a state composed only of uninfected mosquitoes exists and is asymptotically stable.
- A basic offspring number for infected mosquitoes must be greater than 1, to ensure the settlement of the population of infected mosquitoes. An equilibrium, representing a state composed only of infected mosquitoes exists and is asymptotically stable.
- In the preceding case, a third unstable equilibrium exists in the positive orthant. This equilibrium represent a state of coexistence between infected and uninfected mosquitoes.
- With biological sensible parameters the last case occurs.
- With biological parameters the data produced by our model are in excellent agreement with the data from the Cairn trial [39].

This behavior is reminiscent of the competitive exclusion principle. But our model have some completely new properties when considered as an epidemiological model. We have a DFE and we can compute a basic reproduction number $\mathcal{R}_0$ for *Wolbachia* infection. Due to the characteristic of the infection $\mathcal{R}_0 < 1$. However a second equilibrium does exist and is asymptotically stable. We have a backward bifurcation, where a second equilibrium exists when $\mathcal{R}0 < 1$ [2, 10, 73, 20, 30, 31]. We have some competitive exclusion-like situation : namely, depending of the initial condition, only one species survive. This occurs in epidemiological models[11, 43], but in these cases, two equilibria exist and only one is globally asymptotically stable. Considered as an epidemiological model, the peculiarity is that the transmission is only maternally inherited and the behavior is original. To our knowledge this is the first example of the study of a 'vertical only' transmission model. The existence of backward bifurcation, for such a model, is also new.

This paper is organized as follows : In section 2 we study the population dynamics of a population of *aedes aegypti*, incorporating the Egg, Pupae, larvae, immature and mature female. The rationale for the the introduction of two stages in female is to model, in the sequel, the cytoplasmic incompatibility induced by *Wolbachia* infection. We analyze completely this model. Section 3 is devoted to a complete model adapted for the characteristics of *Wolbachia*. A complete analysis is given and bistability and backward bifurcation are proven. Section 4 couples the model of section 3 with a transmission model of dengue of type $SEIR - SI$. We compute a threshold for asymptotic stability for the disease (dengue) free equilibrium. We compare this threshold with a model free of *Wolbachia*. The next section use multi scaling to obtain simpler models and compare with some results in the literature [5, 71]. Finally section 6 explore numerically the feasibility of the sustainable introduction of *Wolbachia* and control of dengue. We finish by a conclusion.

2 Population dynamics of wild *aedes* mosquito

Before presenting and analyzing the model of infection with *Wolbachia* we will need some preliminaries and some results will be used in the sequel.

2.1 The model

The life cycle of a mosquito consists of two main stages: aquatic (egg, larva, pupa) and adult (with males and females). After emergence from pupa, a female mosquito needs to mate and get a blood meal before it starts laying eggs. Then every $4 - -5$ days it will take a blood meal and lay $100 - -150$ eggs at different places ($10 - -15$ per place). For the mathematical description, our model is inspired by the model considered in [19, 1].

However we will consider three aquatic stages, where the authors [19, 1] lump the three stages into a single aquatic stage. The rationale is to prepare for a subsequent model with infection by *Wolbachia*. Furthermore, we split the adult stage into three sub-compartments, males, immature female and mature female which leads to the following compartments:

- Eggs E;
- Larvae L;
- Pupae P;
- Males M;
- Young immature females Y; We consider a female to be in the Y compartment from its emergence from pupa until her gonotrophic cycle has began, that is the time of mating and taking the first blood meal, which takes typically $3 - -4$ days.
- Mature females F, i.e., fertilized female. A female needs to mate successfully only once and rarely remate [36] .

The parameters μ_E, μ_P, μ_Y, μ_F and μ_M are respectively the death rate of eggs, larvae, pupae, immature female, mature females and males. The parameters η_E,η_L, η_P , β are the respective rate of transfer to the next compartment. The parameter ν is the sex ratio. In this model, we use a density dependent death rate for the larvae stage since mosquitoes larvae (anopheles and aedes) are density sensitive, which imply an additional density mortality rate $\mu_2\, L$ [4, 21, 28, 49, 67, 77]. The equation for L can be considered as a logistic equation. Such an hypothesis is appropriate since mosquitoes only have access to a finite number of potential breeding sites, and density-dependent larval survival has been demonstrated at such sites. The parameter ϕ is the average amount of eggs laid per fertilized female per unit of time.

Mating is a complex process that is not fully understood. However, as discussed in [1] and references therein, the male mosquito can mate practically through all its life. A female mosquito needs one successful mating to breed lifelong [41]. It is admitted that mosquitoes locate themselves in space and time to ensure they are available to mate. Therefore, it is reasonable to assume that in any case the immature female will mate and afterwards move to compartment F , or die. Thus a parameter like $\frac{1}{\beta+\mu_Y}$ can represents the mean time given by length of the first gonotrophic cycle of a female, i.e., the interval from immediately after the mating to the first blood meal.

We assume that all the parameters are constant. In reality, the mosquito population varies

seasonally. Nevertheless, such a model should be a good approximation for a definite season.

$$\begin{cases} \dot{E} &= \phi\, F - (\mu_E + \eta_E)\, E \\ \dot{L} &= \eta_E\, E - (\mu_L + \eta_L + \mu_2\, L)\, L \\ \dot{P} &= \eta_L\, L - (\mu_P + \eta_P)\, P \\ \dot{Y} &= \nu\, \eta_P\, P - (\beta + \mu_Y)\, Y \\ \dot{F} &= \beta\, Y - \mu_F\, F \\ \dot{M} &= (1-\nu)\, \eta_P\, P - \mu_M\, M. \end{cases} \tag{1}$$

If we denote by X a vector of the state space of this systems.

$$X^T = (E, L, P, Y, F, M),$$

then the systems can be written

$$\dot{X} = A(X)\, X,$$

For (1) the matrix is given by

$$A(X) = \begin{bmatrix} -(\mu_E + \eta_E) & 0 & 0 & 0 & \phi & 0 \\ \eta_E & -(\mu_L + \eta_L + \mu_2\, L) & 0 & 0 & 0 & 0 \\ 0 & \eta_L & -(\mu_P + \eta_P) & 0 & 0 & 0 \\ 0 & 0 & \nu\, \eta_P & -(\beta + \mu_Y) & 0 & 0 \\ 0 & 0 & 0 & \beta & -\mu_F & 0 \\ 0 & 0 & (1-\nu)\, \eta_P & 0 & 0 & -\mu_M \end{bmatrix}.$$

The matrix $A(X)$ is a Metzler matrix, this implies that the nonnegative orthant is positively invariant for (1).
Actually $A(X)$ depends only of L, so we will denote the matrix $A(X)$ simply by $A(L)$.

2.2 Analysis of the model

Computing the Jacobian of (1) gives $J(A(L).X) = A(2\, L)$. This Jacobian is again a Metzler matrix, hence (1) is a monotone system.
Using the concept in demography introduced by Böckh, see [35, 34], we can define a basic offspring number as the mean number of females born from one female during its entire reproductive life. This can be computed using the methods of [17, 74] (where the transmission term is given by $\phi\, F$) or by looking at the equations.
Using (1) shows that

$$\mathcal{R}_{0,\mathrm{offsp}} = \frac{\phi}{\mu_F}\, \frac{\eta_E}{\mu_E + \eta_E}\, \frac{\eta_L}{\mu_L + \eta_L}\, \frac{\nu\, \eta_P}{\mu_P + \eta_P}\, \frac{\beta}{\beta + \mu_Y}.$$

When $\mathcal{R}_{0,\text{offsp}} \leq 1$ the only equilibrium is the origin. When $\mathcal{R}_{0,\text{offsp}} > 1$ a second positive equilibrium exists $(E^*, L^*, P^*, Y^*, F^*, M^*)^T$.
We can express all the components as positive linear expressions of P^*

$$L^* = \frac{\mu_p + \eta_p}{\eta_L} P^*, \qquad Y^* = \frac{\nu\,\eta_P}{\beta + \mu_Y} P^*, \tag{2}$$

$$F^* = \frac{\beta}{\beta + \mu_Y} \frac{\nu\,\eta_P}{\mu_F} P^*, \qquad M^* = \frac{(1-\nu)\,\eta_P}{\mu_M} P^* \tag{3}$$

$$E^* = \frac{\phi}{\mu_E + \eta_E} \frac{\beta}{\beta + \mu_Y} \frac{\nu\,\eta_P}{\mu_F} P^*. \tag{4}$$

Finally, replacing in the equation $\dot{L} = 0$, we get

$$\begin{aligned} P^* &= \frac{\eta_L\,(\mu_L + \eta_L)}{\mu_2\,(\mu_P + \eta_P)} \left(\frac{\eta_E\,\nu\,\phi\,\eta_L\,\eta_P}{\mu_F\,(\mu_E + \eta_E)\,(\mu_L + \eta_L)\,(\mu_P + \eta_P)} - 1 \right) \\ &= \frac{\eta_L\,(\mu_L + \eta_L)}{\mu_2\,(\mu_P + \eta_P)}\,(\mathcal{R}_{0,\text{offsp}} - 1) > 0. \end{aligned} \tag{5}$$

For a future use we will need positively compact invariant sets for (1) when $\mathcal{R}_{0,\text{offsp}} > 1$ and when $\mathcal{R}_{0,\text{offsp}} \leq 1$. We will use the classical notations for the order on $\mathbb{R}^n$, i.e., $\leq, , <, \ll$ [38, 65]. In accordance with these notations the closed order interval $[a, b]$ is

$$\big[\, a, b \,\big] = \{x \in \mathbb{R}^n \mid a \leq x \leq b\}$$

We will also denote by $X^* = (E^*, L^*, P^*, Y^*, F^*, M^*)^T \gg 0$.

Proposition 2.1
For any s and any θ such that $0 < s < 1$ and $1 < \theta$ the closed order intervals

$$[\, s\,X^*,\ \theta\,X^* \,]$$

are positively compact invariant set of the positive orthant for system (1) when $\mathcal{R}_{0,offsp} > 1$.

When $\mathcal{R}_{0,offsp} \leq 1$ we take L_k sufficiently large so that

$$\frac{(\mu_L + \eta_L + \mu_2\,L_k)\,L_k}{\mu_L + \eta_L} > 8\,\mathcal{R}_{0,offsp},$$

and then define

$$E_k = \frac{(\mu_L + \eta_L + \mu_2\,L_k)\,L_k}{2\,\eta_E}, \qquad F_k = \frac{\mu_E + \eta_E}{2\phi}\,E_k,$$

$$Y_k = \frac{\mu_F}{2\,\beta}\,F_k, \qquad P_k = \frac{\beta + \mu_Y}{2\,\nu\,\eta_P}\,Y_k,$$

$$M_k = \frac{2\,(1-\nu)\,\eta_P}{\mu_M}\,P_k.$$

If we denote by $X_k = (E_k, L_k, P_k, Y_k, F_k, M_k)^T \in \mathbb{R}^6_+$, then the closed order interval $[0\,, \theta\,X_k]$ is a positively compact invariant set.

Proof
We remark that the vector field associated to (1), $A(X)\,X = f(X)$, is strictly sublinear. In other words this means that for any $X \gg 0$ and any $0 < \lambda < 1$ we have

$$\lambda\, f(X) < f(\lambda\, X).$$

From sublinearity we immediately obtain $f(s\,P^*) > 0$ and $f(\theta\,P^*) < 0$. Using the proof of Proposition 2.1 (page 34 of [65]) we then obtain that $[\,s\,X^*,\ \theta\,X^*\,]$ is positively invariant by the monotone system (1).
When $\mathcal{R}_{0,\mathrm{offsp}} \leq 1$, a straightforward computation yields

$$\begin{aligned}
\dot{P}(X_k) &= \eta_L\, L_k - (\mu_P + \eta_P)\, P_k \\
&= \eta_L\, L_k - (\mu_P + \eta_P)\, \frac{\beta + \mu_Y}{2\,\nu\,\eta_P}\, \frac{\mu_F}{2\,\beta}\, \frac{\mu_E + \eta_E}{2\,\phi}\, \frac{(\mu_L + \eta_L + \mu_2\, L_k)\, L_k}{2\,\eta_E} \\
&= \eta_L\, L_k\, \frac{1}{8\,\mathcal{R}_{0,\mathrm{offsp}}} \left[8\,\mathcal{R}_{0,\mathrm{offsp}} - \frac{(\mu_L + \eta_L + \mu_2\, L_k)}{\mu_L + \eta_L} \right] < 0
\end{aligned}$$

and finally $f(X_k) \ll 0$. With $f(0) = 0$ the preceding argument shows that $[0\,, \theta\, X_k]$ is a positively invariant compact set.

■

We can now give the main result of this section

Theorem 2.1
If $\mathcal{R}_{0,offsp} \leq 1$ the origin is globally asymptotically stable in the nonnegative orthant $\mathbb{R}^n_+$. In other words the mosquito population goes to extinction.
If $\mathcal{R}_{0,offsp} > 1$ the positive equilibrium X^* is globally asymptotically stable on the nonnegative orthant minus the P-axis, $\mathbb{R}^n_+ \setminus \{P | P = 0\}$.

Proof
We assume that $\mathcal{R}_{0,\mathrm{offsp}} \leq 1$ and we consider the Lyapunov function (in Lasalle's sense) on the positively invariant set $[0, \theta\, X_k]$.

$$\begin{aligned}
V(X) = \frac{\eta_E}{\mu_E + \eta_E}\, E + L + \frac{\nu\,\eta_P\,\beta\,\eta_E\,\phi}{(\mu_E + \eta_E)\,(\beta + \mu_Y)\,(\mu_P + \eta_P)\,\mu_F}\, P \\
+ \frac{\beta\,\eta_E\,\phi}{(\mu_E + \eta_E)\,(\beta + \mu_Y)\,\mu_F}\, Y + \frac{\eta_E\,\phi}{(\mu_E + \eta_E)\,\mu_F}\, F
\end{aligned}$$

We obtain

$$\dot{V}(X) = (\mu_L + \eta_L)\ [\mathcal{R}_{0,\mathrm{offsp}} - 1]\ L - \mu_2\, L^2 \leq 0$$

The largest invariant set contained in the set $L = 0$ or equivalently

$$\{X \in [0, \theta\, X_K] \,|\, \dot{V}(X) = 0\},$$

is clearly the set $\{L = E = F = Y = P = 0\}$, in other words the M-axis contained in $[0, \theta X_k]$. But the only set invariant in this subset is $\{0\}$. Using the results of Lasalle (corollary 1 of [47] or Theorem 3.7.11, page 346 of [6]) on the set $[0, \theta X_k]$ we obtain the global stability of the origin. Since our compact set can be arbitrarily large, this proves the global asymptotic stability of the origin.

We now assume $\mathcal{R}_{0,\text{offsp}} > 1$. We change variables by letting $X_{\text{new}} = X_{\text{old}} - X^*$. The new system can be written once again as $\dot{X}_{\text{new}} = B(X_{\text{new}})\,.X_{\text{new}}$. For simplicity we use the same coordinates for the new variables. In this setting the matrix B writes

$$B(X) = \begin{bmatrix} -(\mu_E+\eta_E) & 0 & 0 & 0 & \phi & 0 \\ \eta_E & -[\mu_L+\eta_L+\mu_2\,(L+2\,L^*)] & 0 & 0 & 0 & 0 \\ 0 & \eta_L & -(\mu_P+\eta_P) & 0 & 0 & 0 \\ 0 & 0 & \nu\,\eta_P & -(\beta+\mu_Y) & 0 & 0 \\ 0 & 0 & 0 & \beta & -\mu_F & 0 \\ 0 & 0 & (1-\nu)\,\eta_P & 0 & 0 & -\mu_M \end{bmatrix}.$$

We consider the positively invariant set (for the new coordinates)

$$[(s-1)\,X^*, (\theta-1)\,X^*].$$

This set contains one equilibrium, namely the origin. The remaining equilibrium is $-X^*$.
We will construct a vector $X_c \gg 0$ such that $B(X)\,X_c \gg 0$.
First we choose $L_c = L^*$ and then

$$E_c = E^* + \frac{s\,\mu_2}{2\,\eta_E}\,L^*\,X^*, \qquad F_c = F^* + \frac{s\,\mu_2\,(\mu_E+\eta_E)}{4\,\eta_E\,\phi}\,L^*\,X^*,$$
$$Y_c = Y^* + \frac{s\,\mu_2\,\mu_F\,(\mu_E+\eta_E)}{8\,\eta_E\,\phi\,\beta}\,L^*\,X^*, \qquad P_c = P^* + \frac{(s\,\beta+\mu_Y)\mu_2\,\mu_F\,(\mu_E+\eta_E)}{16\,\nu\,\eta_P\,\eta_E\,\phi\,\beta}\,L^*\,X^*,$$
$$M_c = \frac{2\,(1-\nu)\,\eta_P}{\mu_M}\,P_c.$$

We have $B(X)\,X_c \ll 0$ in the positively invariant compact set $[(1-s)\,X^*, (\theta-1)\,X^*]$.
Since $B(X)$ is a Metzler matrix, we can apply Theorem 8.6 (ii), page 36 of [48] to conclude that the origin is globally asymptotically stable in the closed order interval $[(1-s)\,X^*, (\theta-1)\,X^*]$. This proves that X^* is globally asymptotically stable in the positive orthant. The only invariant face for system (1) is the M-axis, which ends the proof of our result.

■

For further reference we will denote the vector field on $\mathbb{R}^6$ associated to (1) by $f(X, \phi, \mu_F, \mu_M)$. This is to stress some particular parameters which will be of importance later on.

3 A complete model

We will now consider a model of infection of *Wolbachia* in an *Aedes* population. We assume that the wild population, when *Wolbachia* is not present, is sustainable. This means that $\mathcal{R}_{0,\text{offsp}} > 1$.
Our model take into account cytoplasmic incompatibility, which is outlined in the following table :

Table 1: Cytoplasmic incompatibility

Reproduction			
		♂	
		Infected	Uninfected
♀	Infected	Infected	Infected
	Uninfected	Sterile	Uninfected

We index by U or W respectively the uninfected and infected stages. With this notation, the compartment of F_{WU} is the compartment of infected females fertilized by uninfected males, F_{WW} the compartment of infected females fertilized by infected males, F_{UU} the females resulting of mating between uninfected individuals and finally F_{UW} is the uninfected female fecundated by an infected male. We assume that cytoplasmic incompatibility is complete and this implies that this last compartment is constituted with sterile females. The assumption of complete CI is consistent with laboratory data [76]. Furthermore, based on this data, we also assume perfect maternal transmission of w Mel infection.

These assumptions lead to the following system, defined on a subset of $\mathbb{R}^{14}_+$. We split the system in two subsystems :

$$
\begin{cases}
\dot{E}_U &= \phi\, F_{UU} - (\mu_E + \eta_E)\; E_U \\
\dot{L}_U &= \eta_E\, E_U - [\eta_L + \mu_L + \mu_2\,(L_U + L_W)\,]\, L_U \\
\dot{P}_U &= \eta_L\, L_U - (\mu_P + \eta_P)\, P_U \\
\dot{Y}_U &= \nu\, \eta_P\, P_U - (\beta + \mu_Y)\, Y_U \\
\dot{F}_{UU} &= \beta\, Y_U\, \dfrac{M_U}{M_U + M_W} - \mu_{FU}\, F_{UU} \\
\dot{M}_U &= (1-\nu)\, \eta_P\, P_U - \mu_{MU}\, M_U \\
\dot{E}_W &= \theta\, \phi\, (F_{WW} + F_{WU}) - (\mu_E + \eta_E)\; E_W \\
\dot{L}_W &= \eta_E\, E_W - [\eta_L + \mu_L + \mu_2\,(L_W + L_U)\,]\, L_W \\
\dot{P}_W &= \eta_L\, L_W - (\mu_P + \eta_P)\, P_W \\
\dot{Y}_W &= \nu\, \eta_P\, P_W - (\beta + \mu_Y)\, Y_W \\
\dot{F}_{WU} &= \beta\, Y_W\, \dfrac{M_U}{M_U + M_W} - \mu_{FW}\, F_{WU} \\
\dot{F}_{WW} &= \beta\, Y_W\, \dfrac{M_W}{M_U + M_W} - \mu_{FW}\, F_{WW} \\
\dot{M}_W &= (1-\nu)\, \eta_P\, P_W - \mu_{MW}\, M_W,
\end{cases}
\tag{6}
$$

and

$$
\dot{F}_{UW} = \beta\, Y_U\, \frac{M_W}{M_U + M_W} - \mu_{FU}\, F_{UW}. \tag{7}
$$

Since F_{UW} does not appears in the others equations, the asymptotic behavior of the complete system can be reduced to the behavior of system (6), with (7) discarded. From now on, we will consider this reduced system.

This system (6) is defined on $\mathbb{R}^{13}_+ \setminus \{M_U = M_W = 0\}$. This set is clearly positively invariant.

We make minimal hypotheses on the parameters. We incorporate a reduction of the mean life of the adult male and female mosquito as quoted in the literature [12, 29, 33, 56, 57, 62, 79]. Then we denote by μ_{FW} and μ_{MW} respectively the death rate of female and male infected by *Wolbachia*. We also introduce a competition, for mating, between infected male and uninfected male.

In this model E_U, E_W are the eggs compartments, respectively uninfected and infected. According to the literature, there is no apparent difference between infected and uninfected eggs [50] . So we denote respectively by μ_E and η_E the common death rate and the transition into the larvae compartments.

Similarly L_U and L_W are the larval compartments. In this case we introduce an intraspecific competition between larvae. Again, it seems that there is no known difference between infected

and uninfected larvae [50]. Then we denote by μ_L and η_L the common death rate and transition rate to pupae compartments.
We denote by P_U and P_W the uninfected and infected pupae compartments.
We also introduce a factor $\theta \leq 1$ to consider an eventual decrease of the amount of laid eggs by an infected female [40, 55, 56, 76, 79].
We consider this model in the nonnegative orthant minus the set defined by $\{M_U = M_W = 0\}$. The nonnegative orthant is clearly positively invariant by this system. We can define the value of our system to be 0 at the origin, since the absence of population is a singular point. Note that our vector field cannot be prolongated continuously on the nonnegative orthant. However all the trajectories are defined on our domain. The competition between males results in the loss of monotonicity.

3.1 Equilibria

3.1.1 Uninfected equilibrium : *Wolbachia* Free equilibrium

When there is no infection in the mosquito population , i.e., $E_W = L_W = P_W = Y_W = F_{WU} = F_{WW} = F_{UW} = M_W = 0$, model (6) reduce to model (1) of mosquito population. Then in the sequel we will assume that $\mathcal{R}_{0,\text{offsp}} > 1$. For this model the basic offspring number is

$$\mathcal{R}_{0,\text{offsp},U} = \frac{\phi}{\mu_{FU}} \frac{\eta_E}{\mu_E + \eta_E} \frac{\eta_L}{\mu_L + \eta_L} \frac{\nu\,\eta_P}{\mu_P + \eta_P} \frac{\beta}{\beta + \mu_Y}.$$

In this case there is an equilibrium on the boundary of the nonnegative orthant whose components are given by (2, 5), with the evident adaptation of notations corresponding to the vector field $f(X, \phi, \mu_{FU}, \mu_{MU})$.
This equilibrium corresponds to a population free of infection. We will denote this equilibrium by WFE (*Wolbachia* free equilibrium).

3.1.2 Completely *Wolbachia*-Infected equilibrium

In a similar way if $E_U = L_U = P_U = Y_U = F_{UU} = M_U = 0$ the system reduce to a system like (1) with different parameters. Actually this corresponds to the vector field $f(\theta\,\phi, \mu_{FW}, \mu_{MW})$. Then we define a basic offspring number for the completely infected population

$$\mathcal{R}_{0,\text{offsp},W} = \frac{\theta\,\phi}{\mu_{FW}} \frac{\eta_E}{\mu_E + \eta_E} \frac{\eta_L}{\mu_L + \eta_L} \frac{\nu\,\eta_P}{\mu_P + \eta_P} \frac{\beta}{\beta + \mu_Y}.$$

In this case there is an equilibrium on the boundary of the nonnegative orthant given by

$$P_W^* = \frac{\eta_L\,(\mu_L + \eta_L)}{\mu_2\,(\mu_P + \eta_P)}\,(\mathcal{R}_{0,\text{offsp},W} - 1) \tag{8}$$

$$L_W^* = \frac{\mu_p + \eta_p}{\eta_L}\,P_W^*, \qquad Y_W^* = \frac{\nu\,\eta_P}{\beta + \mu_Y}\,P_W^*, \tag{9}$$

$$F_{WW}^* = \frac{\beta}{\beta + \mu_Y} \frac{\nu\,\eta_P}{\mu_{FW}}\,P_W^*, \qquad M_W^* = \frac{(1-\nu)\,\eta_P}{\mu_{MW}}\,P_W^* \tag{10}$$

$$E_W^* = \frac{\theta\,\phi}{\mu_E + \eta_E} \frac{\beta}{\beta + \mu_Y} \frac{\nu\,\eta_P}{\mu_{FW}}\,P_W^*, \qquad F_{WU}^* = 0 \qquad F_{UW}^* = 0 \tag{11}$$

In the sequel, we will refer to this equilibrium as the “Completely *Wolbachia*-Infected Equilibrium" (CWIE).

Since we are addressing the issue of the sustainable establishment of *Wolbachia* we will assume what follows that $\mathcal{R}_{0,\text{offsp},W} > 1$.

3.1.3 A coexistence equilibrium

We remark that

$$\mathcal{R}_{0,\text{offsp},W} = \frac{\theta\,\mu_{FU}}{\mu_{FW}}\,\mathcal{R}_{0,\text{offsp},U} < \mathcal{R}_{0,\text{offsp},U}.$$

We assume that $\mathcal{R}_{0,\text{offsp},W} > 1$. In this case a coexistence equilibrium exists in the positive orthant. The components P_U and P_W are given by

$$P_{U,\text{coex}} = \frac{\eta_L\,\theta\,\mu_{FU}\,\mu_{MU}\,(\mu_L+\eta_L)}{\mu_2\left[\mu_{MW}\,(\mu_{FW}-\theta\,\mu_{FU})+\theta\,\mu_{MU}\,\mu_{FU}\right](\mu_P+\eta_P)}\,(\mathcal{R}_{0,\text{offsp},W}-1)$$
$$P_{W,\text{coex}} = \frac{\eta_L\,\mu_{MW}\,(\mu_{FW}-\theta\,\mu_{FU})\,(\mu_L+\eta_L)}{\mu_2\left[\mu_{MW}\,(\mu_{FW}-\theta\,\mu_{FU})+\theta\,\mu_{MU}\,\mu_{FU}\right](\mu_P+\eta_P)}\,(\mathcal{R}_{0,\text{offsp},W}-1)$$

These two components are positive with our hypotheses. The remaining components can be expressed in terms of these two as follows:

$$M_{U,\text{coex}} = \frac{(1-\nu)\,\eta_P}{\mu_{MU}}\,P_{U,\text{coex}}, \qquad M_{W,\text{coex}} = \frac{(1-\nu)\,\eta_P}{\mu_{MW}}\,P_{W,\text{coex}},$$
$$L_{U,\text{coex}} = \frac{\mu_P+\eta_P}{\eta_L}\,P_{U,\text{coex}}, \qquad L_{W,\text{coex}} = \frac{\mu_P+\eta_P}{\eta_L}\,P_{W,\text{coex}},$$
$$Y_{U,\text{coex}} = \frac{\nu\,\eta_P}{\beta+\mu_Y}\,P_{U,\text{coex}} \qquad Y_{W,\text{coex}} = \frac{\nu\,\eta_P}{\beta+\mu_Y}\,P_{W,\text{coex}}$$

$$F_{UU,\text{coex}} = \frac{\beta\,\nu\,\eta_P\mu_{MW}}{\mu_{FU}\,(\mu_{MU}\,P_{W,\text{coex}}+\mu_{MW}\,P_{U,\text{coex}})\,(\beta+\mu_Y)}\,P^2_{U,\text{coex}},$$
$$F_{WW,\text{coex}} = \frac{\beta\,\nu\,\eta_P\mu_{MU}}{\mu_{FW}\,(\mu_{MU}\,P_{W,\text{coex}}+\mu_{MW}\,P_{U,\text{coex}})\,(\beta+\mu_Y)}\,P^2_{W,\text{coex}},$$
$$F_{WU,\text{coex}} = \frac{\beta\,\nu\,\eta_P\mu_{MW}}{\mu_{FW}\,(\mu_{MU}\,P_{W,\text{coex}}+\mu_{MW}\,P_{U,\text{coex}})\,(\beta+\mu_Y)}\,P_{W,\text{coex}}\,P_{U,\text{coex}},$$
$$F_{UW,\text{coex}} = \frac{\beta\,\nu\,\eta_P\mu_{MU}}{\mu_{FW}\,(\mu_{MU}\,P_{W,\text{coex}}+\mu_{MW}\,P_{U,\text{coex}})\,(\beta+\mu_Y)}\,P_{W,\text{coex}}\,P_{U,\text{coex}},$$
$$E_{U,\text{coex}} = \frac{\beta\,\nu\,\eta_P\mu_{MW}\,\phi}{\mu_{FU}\,(\mu_{MU}\,P_{W,\text{coex}}+\mu_{MW}\,P_{U,\text{coex}})\,(\beta+\mu_Y)\,(\mu_E+\eta_E)}\,P^2_{U,\text{coex}},$$
$$E_{W,\text{coex}} = \frac{\beta\,\nu\,\eta_P\,\theta\,\phi}{\mu_{FW}\,(\beta+\mu_Y)\,(\mu_E+\eta_E)}\,P_{W,\text{coex}}.$$

3.2 Forward boundedness of the trajectories

In this section we will prove that all the trajectories are forward bounded and that when $\mathcal{R}_{0,\text{offsp},W} > 1$ the trajectories cannot approach the manifold on which the system is not defined.

We define

$$\begin{aligned} E &= E_U + E_W, & L &= L_U + L_W, \\ Y &= Y_U + Y_W, & M &= M_U + M_W, \\ F &= F_{WW} + F_{UU} + F_{WU}. \end{aligned}$$

Under our assumptions, we have

$$\phi\, F - (\mu_E + \eta_E)\, E \geq \dot{E}$$

$$\eta_E\, E - [\mu_L + \eta_L + \mu_2\, L]\, L = \dot{L}$$

$$\eta_L\, L - (\mu_P + \eta_P)\, P_U = \dot{P}$$

$$\nu\, \eta_P\, L - (\mu_P + \eta_P)\, P = \dot{Y}$$

$$\beta_Y\, Y - \mu_{FU}\, F \geq F$$

$$(1 - \nu)\, \eta_P\, P - \mu_{MU}\, M \geq \dot{M}.$$

The left hand sides of these inequalities correspond to the vector field $f(\phi, \mu_{MU}, \mu_{FU})$.
From proposition (2.1) we know that either $[sX^*, \theta\, X^*]$ is positively invariant in $\mathbb{R}^6_+$, when $\mathcal{R}_{0,\text{offsp},W} > 1$, or $[0, \theta\, X_k]$ is positively invariant when $\mathcal{R}_{0,\text{offsp},W} \leq 1$.
In any case we have a positively invariant compact set that is arbitrarily large. We denote by K this set. The upper boundaries of these sets are constituted of a certain number of faces F_i, $i = 1, \ldots, 6$, that arer parallel to the axis. The invariance can be expressed, using the inner product, by

$$\langle f(\theta\, \phi, \mu_{MW}, \mu_{FW}) \mid e_i \rangle \leq 0,$$

for any $X \in F_i$ and e_i belonging to the canonical basis of $\mathbb{R}^6$. By the preceding inequalities we have, on the upper faces of the order intervals

$$\left\langle (E, L, Y, F, M)^T \mid e_i \right\rangle \leq 0.$$

This proves that the trajectories cannot escape by the upper faces of the order interval. This proves that any trajectory is forward bounded.

3.3 Stability Analysis of the equilibria

3.3.1 Stability of the *Wolbachia* Free Equilibrium

To study the stability of the infection free equilibrium WFE we compute the basic reproduction ratio for the infection by *Wolbachia*. The variable are solitude in those corresponding to uninfected compartments i.e.,

$$E_U, L_U, P_U, Y_U, F_{UU}, M_U,$$

and the others variables for infected compartments

$$E_W, L_W, P_W, Y_W, F_{WW}, F_{WU}, F_{UW}, M_W.$$

As remarked above, since F_{UW} does not appear in the other equation and is decoupled from the system, we can discard the equation on $\dot{F}_{UW}$.
We use the technique of [74] to compute the basic reproduction ratio for *Wolbachia*.

Since we are dealing with 13 equations, the verification of the hypothesis (A5) of [74] is not completely straightforward : we have to prove that, when the transmission is set to zero, then the Jacobian of the resulting system, computed at the WFE, is a stable matrix (by stable we means Hurwitz). Setting the transmission to zero amounts to set $\theta = 0$. It is well known that the Jacobian computed at the WFE is a diagonal block upper triangular matrix :

$$\mathrm{Jac}(WFE) = \begin{bmatrix} A_{11} & A_{12} \\ 0 & A_{22} \end{bmatrix}.$$

In the present case A_{11} is a 6×6 matrix and A_{22} is a 7×7 matrix.
The matrix A_{22} when $\theta = 0$ is equal to

$$A_{22} = \begin{bmatrix} -(\eta_E + \mu_E) & 0 & 0 & 0 & 0 & 0 & 0 \\ \eta_E & -(\mu_L + \eta_L)\,\mathcal{R}_{0,\mathrm{offsp},U} & 0 & 0 & 0 & 0 & 0 \\ 0 & \eta_L & -(\eta_P + \mu_P) & 0 & 0 & 0 & 0 \\ 0 & 0 & \nu\eta_P & -(\beta + \mu_Y) & 0 & 0 & 0 \\ 0 & 0 & 0 & \beta & -\mu_{\mathrm{FW}} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\mu_{\mathrm{FW}} & 0 \\ 0 & 0 & (1-\nu)\eta_P & 0 & 0 & 0 & -\mu_{\mathrm{MW}} \end{bmatrix}, \quad (12)$$

and is clearly stable.

We now consider A_{11}

$$A_{11} = \begin{bmatrix} -(\eta_E + \mu_E) & 0 & 0 & 0 & \phi & 0 \\ \eta_E & (\mu_L + \eta_L)(1 - 2\,\mathcal{R}_{0,\mathrm{offsp},U}) & 0 & 0 & 0 & 0 \\ 0 & \eta_L & -(\eta_P + \mu_P) & 0 & 0 & 0 \\ 0 & 0 & \nu\eta_P & -\beta & 0 & 0 \\ 0 & 0 & 0 & \beta & -\mu_{\mathrm{FU}} & 0 \\ 0 & 0 & (1-\nu)\,\eta_P & 0 & 0 & -\mu_{\mathrm{MU}} \end{bmatrix}$$

.
The matrix A_{11} is a Metzler matrix. We can apply a lemma from [44], which we recall for the convenience of the reader

Lemma 3.1
Let $\mathbf{M}$ *be a Metzler matrix, which is block decomposed :*

$$\mathbf{M} = \begin{bmatrix} \mathbf{A} & \mathbf{B} \\ \mathbf{C} & \mathbf{D} \end{bmatrix}.$$

Where $\mathbf{A}$ *and* $\mathbf{D}$ *are square matrices.*
Then $\mathbf{M}$ *is Hurwitz if and only if* $\mathbf{A}$ *and* $\mathbf{D} - \mathbf{C}\mathbf{A}^{-1}\mathbf{B}$ *are Metzler stable.*

We can now prove that A_{11} is Hurwitz. Since we have an evident eigenvalue $-\mu_{\mathrm{MS}}$ in position $(6, 6)$; we can reduce the stability to the stability of the 5×5 principal upper block.

$$V5 = \begin{bmatrix} -(\eta_E + \mu_E) & 0 & 0 & 0 & \phi \\ \eta_E & (\mu_L + \eta_L)(1 - 2\,\mathcal{R}_{0,\mathrm{offsp},U}) & 0 & 0 & 0 \\ 0 & \eta_L & -(\eta_P + \mu_P) & 0 & 0 \\ 0 & 0 & \nu\eta_P & -(\beta + \mu_Y) & 0 \\ 0 & 0 & 0 & \beta & -\mu_{\mathrm{FU}} \end{bmatrix}.$$

If we define $A = V5(1:4, 1:4)$, the first upper 4×4 block of $V5$ and the other blocks accordingly. Since the block A is lower triangular with a negative diagonal, we have the stability of this block. A computation of $D - C\,A^{-1}\,B$, with this block decomposition, yields after some simplifications

$$D - C\,A^{-1}\,B = \mu_{FU}\,\frac{1 - \mathcal{R}_{0,\mathrm{offsp},U}}{2\,\mathcal{R}_{0,\mathrm{offsp},U} - 1} < 0.$$

Which proves that A_{11} is Hurwitz and finally that the hypothesis (A5) is satisfied.
We can now compute the basic reproduction ratio for *Wolbachia* infection. We denote by F the Jacobian of all the transmission term in the infected compartments
We denote by V the part of the Jacobian A_{22} computed at the WFE

$$F = \begin{bmatrix} 0 & 0 & 0 & 0 & \theta\,\phi & \theta\,\phi & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

We denote by V the part of the Jacobian A_{22} computed at the WFE of the remaining terms. Actually $V = A_{22}$ given in (12).
We have $\mathcal{R}_{0,W} = \rho(-F\,V^1)$. An immediate computation gives

$$-F\,V^{-1} = \begin{bmatrix} \frac{\theta\,\mu_{\mathrm{FU}}}{\mu_{\mathrm{FW}}} & \frac{\theta\,(\eta_E + \mu_E)\,\mu_{\mathrm{FU}}}{\eta_E\,\mu_{\mathrm{FW}}} & \frac{\theta\,\phi\,\beta\,\nu\,\eta_P}{\mu_{\mathrm{FW}}\,(\mu_P + \eta_P)\,(\beta + \mu_Y)} & \frac{\theta\,\phi\,\beta}{\mu_{\mathrm{FW}}\,(\beta + \mu_Y)} & \frac{\theta\,\phi}{\mu_{\mathrm{FW}}} & \frac{\theta\,\phi}{\mu_{\mathrm{FW}}} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

Finally

$$\mathcal{R}_{0,W} = \frac{\theta\,\mu_{\mathrm{FU}}}{\mu_{\mathrm{FW}}} < 1.$$

This proves that the WFE is locally asymptotically stable.

3.3.2 Stability of the Completely *Wolbachia*-Infected Equilibrium

In this section, for the existence of the CWIE, we assume

$$1 < \mathcal{R}_{0,\mathrm{offsp},W} = \mathcal{R}_{0,W}\;\mathcal{R}_{0,\mathrm{offsp},U} < \mathcal{R}_{0,\mathrm{offsp},U}.$$

The Jacobian computed at the CWIE is a block diagonal lower triangular matrix.

$$\mathrm{Jac}(CWIE) = \begin{bmatrix} A_{11} & A_{12} \\ 0 & A_{22} \end{bmatrix}.$$

We have

$$A_{11} = \begin{bmatrix} -(\eta_E+\mu_E) & 0 & 0 & 0 & \phi & 0 \\ \eta_E & -(\beta+\mu_Y)\,(\mu_L+\eta_L)\,\mathcal{R}_{0,\mathrm{offsp},W} & 0 & 0 & 0 & 0 \\ 0 & \eta_L & -(\eta_P+\mu_P) & 0 & 0 & 0 \\ 0 & 0 & \nu\eta_P & -(\beta+\mu_Y) & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu_{\mathrm{FU}} & 0 \\ 0 & 0 & (1-\nu)\,\eta_P & 0 & 0 & -\mu_{\mathrm{MU}} \end{bmatrix}.$$

The elements of the diagonal are clearly eigenvalues of A_{11}, hence this block is Hurwitz.
We consider now A_{22}

$$A_{22} = \begin{bmatrix} -(\eta_E+\mu_E) & 0 & 0 & 0 & \theta\phi & \theta\phi & 0 \\ \eta_E & (\mu_L+\eta_L)\,(1-2\,\mathcal{R}_{0,\mathrm{offsp},W}) & 0 & 0 & 0 & 0 & 0 \\ 0 & \eta_L & -(\eta_P+\mu_P) & 0 & 0 & 0 & 0 \\ 0 & 0 & \nu\eta_P & -(\beta+\mu_Y) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu_{\mathrm{FW}} & 0 & 0 \\ 0 & 0 & 0 & \beta & 0 & -\mu_{\mathrm{FW}} & 0 \\ 0 & 0 & -(\nu-1)\eta_P & 0 & 0 & 0 & -\mu_{\mathrm{MW}} \end{bmatrix}.$$

The matrix A_{22} is Hurwitz if and only if the upper principal 5×5 block A_{111} is stable.

$$A_{111} = \begin{bmatrix} -(\eta_E+\mu_E) & 0 & 0 & 0 & \theta\phi & \theta\phi \\ \eta_E & (\mu_L+\eta_L)\,(1-2\,\mathcal{R}_{0,\mathrm{offsp},W}) & 0 & 0 & 0 & 0 \\ 0 & \eta_L & -(\eta_P+\mu_P) & 0 & 0 & 0 \\ 0 & 0 & \nu\eta_P & -(\beta+\mu_Y) & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu_{\mathrm{FW}} & 0 \\ 0 & 0 & 0 & \beta & 0 & -\mu_{\mathrm{FW}}. \end{bmatrix}$$

We will use again lemma (3.1) for the stability of Metzler matrices. With the notation of the lemma, we choose for A the upper principal 4×4 block. This block is a lower triangular matrix with negative diagonal elements, hence stable.
A straightforward computation, after arrangements, gives

$$D - C\,A^{-1}\,B = \begin{bmatrix} -\mu_{FW} & 0 \\ \mu_{FW}\,\dfrac{\mathcal{R}_{0,\mathrm{offsp},W}}{2\,\mathcal{R}_{0,\mathrm{offsp},W}-1} & -\mu_{FW}\,\dfrac{(\mathcal{R}_{0,\mathrm{offsp},W}-1)}{(2\,\mathcal{R}_{0,\mathrm{offsp},W}-1)} \end{bmatrix},$$

which is clearly a stable Metzler matrix. This proves finally the asymptotic stability of the CWIE.

3.3.3 Stability of the coexistence equilibrium

We compute the determinant of the Jacobian at the coexistence equilibrium. We recall that we have discarded the equation of $\dot{F}_{UW}$, then we are reduced in dimension 13. We obtain after rearrangement and simplifications

$$\begin{aligned}\det(\mathrm{Jac}(Coex)) = \beta\,\theta\,\phi\,\nu\,\eta_P\,\eta_L\,\eta_E\,\mu_{MU}\,\mu_{MW}\,\mu_{FU}\,(\mu_{FW}-\theta\,\mu_{FU})\\ \times(\mu_E+\eta_E)\,(\mu_L+\eta_L)\,(\mu_P+\eta_P)\,(\beta+\mu_Y)\,(\mathcal{R}_{0,\mathrm{offsp},W}-1)>0 \quad (13)\end{aligned}$$

Since we are in an odd dimension, this proves the instability of the coexistence equilibrium.

3.4 Summary of results

- The trajectories of system (6) are forward bounded.
- When $\mathcal{R}_{0,\mathrm{offsp},U}>1$ there exists an equilibrium without infection (WFE) which is asymptotically stable.
- When $\mathcal{R}_{0,W}<\dfrac{1}{\mathcal{R}_{0,\mathrm{offsp},U}}$ only the WFE exists and is globally asymptotically stable on the nonnegative orthant minus the manifold $M_W=0$.
- When $\mathcal{R}_{0,W}\,\mathcal{R}_{0,\mathrm{offsp},U}=\mathcal{R}_{0,\mathrm{offsp},W}>1$ three equilibria exist. The WFE, an equilibrium with the total population infected (CWIE) and a coexistence equilibrium in the positive orthant. The WFE and CWIE are asymptotically stable, the coexistence equilibrium is unstable.

The phenomenon described above is now well known in epidemiological models, this the so-called backward bifurcation. See [2, 10, 73, 20, 30, 31] and references therein. To quote [31] a general mechanism leading to backward bifurcations in epidemic models seems unlikely. Backward bifurcations is known to occur in models with group structure and large differences between groups or models with interacting mechanisms (e.g. Vaccination models or reinfection). Our model does not enter in these categories. We can reduce our model, by lumping variables, to a very simple four dimensional system which also exhibits backward bifurcation. This result adds a new situation to the known ones.

4 Dengue and *Wolbachia*

The aim of this section is to explore the interaction between dengue and the sustainable introduction of *Wolbachia* in a population of *Aedes aegypti*. We will couple system (6) with the classical Dietz-Bailey model of dengue [3, 18] to which we have added a compartment of latent individuals. The Dietz model has been well studied in the literature . [23, 24, 59, 68].
We further split the female mosquitoes into susceptible and infected with dengue. We denote by F_{WUI}, F_{WWI}, F_{UWI} and F_{UUI} respectively the female infected by dengue in each compartment of (6). We keep F_{WU}, F_{WW}, F_{UW} and F_{UU} for the total population. We could have introduced an incubation compartment in the mosquitoes. The inclusion of this extra compartment does not change neither the analysis techniques or behavior of the model. The reduction principle we use, in this case, will lead from a 25 dimensional system to a 5 dimensional model while without this incubation compartment we obtain from a 21 dimensional model a reduced 4 dimensional system.For the sake of simplicity, we will thus omit this extra compartment. There

are four identified strains of dengue, and the model should be considered as holding for each one separately.

A $SEIR - SI$ model of transmission of dengue can be

$$\begin{cases} \dot{S}_h &= \Lambda - \left[\beta_{Wvh}\left(F_{WUI}+F_{WWI}\right)+\beta_{Uvh}\left(F_{UUI}+F_{UWI}\right)\right]\dfrac{S_h}{N_h} - \mu_h\, S_h \\ \dot{E}_h &= \left[\beta_{Wvh}\left(F_{WUI}+F_{WWI}\right)+\beta_{Uvh}\left(F_{UUI}+F_{UWI}\right)\right]\dfrac{S_h}{N_h} - \left(\gamma_h+\mu_h\right)E_h \\ \dot{I}_h &= \gamma_h\, E_h - \left(\delta_h+\mu_h\right)I_h \\ \dot{R}_h &= \delta_h\, I_h - \mu_h\, R_h \\ \dot{F}_{WUI} &= \beta_{Whv}\left(F_{WU}-F_{WUI}\right)\dfrac{I_h}{N_h} - \mu_{FW}\, F_{WUI} \\ \dot{F}_{WWI} &= \beta_{Whv}\left(F_{WW}-F_{WWI}\right)\dfrac{I_h}{N_h} - \mu_{FW}\, F_{WWI} \\ \dot{F}_{UUI} &= \beta_{Uhv}\left(F_{UU}-F_{UUI}\right)\dfrac{I_h}{N_h} - \mu_{FU}\, F_{UUI} \\ \dot{F}_{UWI} &= \beta_{Uhv}\left(F_{UW}-F_{UWI}\right)\dfrac{I_h}{N_h} - \mu_{FU}\, F_{UUI} \end{cases} \tag{14}$$

In this system Λ is the recruitment, N_h the total host population, γ_h the per capita rate at which individuals leave the latent period, δ_h the rate of recovery. the μ with different indices denote the per capita death rate. The parameter β_{Wvh} denotes the transmission from vector to human for *Wolbachia* infected mosquitoes, β_{Whv} is the corresponding transmission from human to vector. The other β parameters are defined similarly. A female in F_{UW} is not infected by *Wolbachia*, this female has only be fecundated by an infected male. It is not known if dengue infection of mosquito modify the death rate, consensus, for wMel being currently that the death rate is not modified.
We assume this hypothesis. However modifications of these hypotheses will not modify the structure of this model and the conclusions will be identical, only the thresholds expressions will be modified.
Mosquitoes with and without *Wolbachia* are equally likely to become infected with dengue. There is currently, no indication of a difference. On the other hand they differ in their ability to transmit, depending of the strain of *Wolbachia* [76]
We will now study the asymptotic behavior of the coupled systems (6 and 14). The variables of (14) does not appear in (6). We have a triangular system. We recall a result of Vidyasagar [75] Theorem 3.1and Theorem 3.5:

Theorem 4.1 *[Vidyasagar]*
Consider the following triangular system, $\mathcal{C}^1$ on a neighborhood of (x^*, y^*) :

$$\begin{cases} \dot{x} = f(x) & x \in \mathbb{R}^n\ , y \in \mathbb{R}^m \\ \dot{y} = g(x,y) & \\ \text{ with an equilibrium point, } (x^*,y^*), \text{ i.e.,} & \\ f(x^*) = 0 \text{ and } g(x^*,y^*) = 0. & \end{cases}$$

If x^* is LAS, if y^* is asymptotically stable for $\dot{y} = g(x^*, y)$ then (x^*, y^*) is asymptotically stable for the complete system.
If x^* is unstable then (x^*, y^*) is unstable for the complete system.

We knows that the CWIE is asymptotically stable for (6), provided
$\mathcal{R}_{0,\text{offsp},W} > 1$. Then to study the stability of the equilibria of the complete system, we can replace in (14) the variable of (6) by their values at the CWIE. Using the values given in (8,9) we get a reduced system

$$\begin{cases} \dot{S}_h & = \Lambda - \beta_{Wvh}\, F_{WWI}\, \dfrac{S_h}{N_h} - \mu_h\, S_h \\ \dot{E}_h & = \beta_{Wvh}\, F_{WWI}\, \dfrac{S_h}{N_h} - (\gamma_h + \mu_h)\, E_h \\ \dot{I}_h & = \gamma_h\, E_h - (\delta_h + \mu_h)\, I_h \\ \dot{N}_h & = \Lambda - \mu_h\, N_h \\ \dot{F}_{WWI} & = \beta_{Whv}\, (F^*_{WW} - F_{WWI})\, \dfrac{I_h}{N_h} - \mu_{FW}\, F_{WWI} \end{cases} \tag{15}$$

We have replaced the equation on R_h by the equation on N_h to obtain an equivalent system. Using again Vydiasagar's Theorem, setting $N^*_h = \dfrac{\Lambda}{\mu_h}$, we have to study the equilibria of the equivalent system

$$\begin{cases} \dot{S}_h & = \Lambda - \beta_{Wvh}\, F_{WWI}\, \dfrac{S_h}{N^*_h} - \mu_h\, S_h \\ \dot{E}_h & = \beta_{Wvh}\, F_{WWI}\, \dfrac{S_h}{N^*_h} - (\gamma_h + \mu_h)\, E_h \\ \dot{I}_h & = \gamma_h\, E_h - (\delta_h + \mu_h)\, I_h \\ \dot{F}_{WWI} & = \beta_{Whv}\, (F^*_{WW} - F_{WWI})\, \dfrac{I_h}{N^*_h} - \mu_{FW}\, F_{WWI} \end{cases} \tag{16}$$

This is a simple model of transmission of dengue, with a latent class.
The basic reproduction ratio for this model is

$$\mathcal{R}_{0,\text{dengue},W} = \frac{\beta_{Wvh}\, \beta_{Whv} F^*_{WW}}{\mu_{FW}}\, \frac{\gamma_h}{(\gamma_h + \mu_h)\, (\delta_h + \mu_h)\, N^*_h}$$

We denote as usual by $\text{DFE}_{\text{dengue}}$ the equilibrium $(N^*_h, 0, 0, 0, 0, 0, 0, 0)$ of (14).

We have proved that $(CWIE, \text{DFE}_{\text{dengue}})$ is an asymptotically stable equilibrium of (6,14) if $\mathcal{R}_{0,\text{dengue},W} > 1$.
The coexistence equilibrium is unstable for (6), then any equilibrium in the form (X^*_{coex}, Y^*) where Y^* is an equilibrium of (14) is unstable by Vydiasagar theorem.
Since we are interested in the control of dengue, we will only consider the equilibria without dengue. We does not provide an analysis of the endemic equilibria, which would be straightforward.

In a similar manner $(WFE, \mathrm{DFE}_{\mathrm{dengue}})$ is an asymptotic equilibrium of (6,14) if $\mathcal{R}_{0,\mathrm{dengue},U} > 1$, where analogously

$$\mathcal{R}_{0,\mathrm{dengue},U} = \frac{\beta_{Uvh}\,\beta_{Uhv}F^*_{UU}}{\mu_{FU}}\,\frac{\gamma_h}{(\gamma_h+\mu_h)\,(\delta_h+\mu_h)\,N^*_h}.$$

Using our formulas we have

$$\mathcal{R}_{0,\mathrm{dengue},W} = \frac{\beta_{Wvh}\,\beta_{Whv}}{\beta_{Uvh}\,\beta_{Uhv}}\,\frac{\mu_{FU}}{\mu_{FW}}\,\frac{\mathcal{R}_{0,\mathrm{offsp},W}-1}{\mathcal{R}_{0,\mathrm{offsp},U}-1}\mathcal{R}_{0,\mathrm{dengue},U}.$$

We have the following result for system (16)

Proposition 4.1
If $\mathcal{R}_{0,dengue,W} \leq 1$ then $(N^*_h, 0, 0, 0)$ the DFE of (16) is globally asymptotically stable.

Proof
The set $K = \{(S_h, E_h, I_h, F_{WWI}) \in \mathbb{R}^3_+ \times [0, F_{W^*}] \mid N_h \leq N\,;\, F_{WWI} \leq F^*_W\}$ is a positively invariant absorbing compact set for the system considered. We consider the following function

$$V((E_h, I_h, F_{WWI}) = \gamma_h\,E_h + (\gamma_h+\mu_h)\,I_h + \beta_{Wvh}\,\frac{\gamma_h}{\mu_{FW}}\,F_{WWI}.$$

We have

$$\begin{aligned}\dot{V} &= \left[-(\gamma_h+\mu_h)\,(\delta_h+\mu_h) + \frac{\beta_{Wvh}\,\beta_{Whv}\,(F^*_{WW}-F_{WWI})\,\gamma_h}{\mu_{FW}\,N^*_h}\,I_h + \beta_{Wvh}\,\gamma_h\,\left[-1+\frac{S_h}{N^*_h}\right]\right]\\ &= -(\gamma_h+\mu_h)\,(\delta_h+\mu_h)\,\left(1-\mathcal{R}_{0,\mathrm{dengue},W}\,(1-\frac{F_{WWI}}{F^*_{WW}}\right) + \beta_{Wvh}\,\gamma_h\,\left[-1+\frac{S_h}{N^*_h}\right] \leq 0\end{aligned}$$

It is clear that the greatest invariant set contained in K and in the set $\dot{V}=0$ is the DFE. Using LaSalle's invariant principle [6, 48, 47] on K, this proves the global asymptotic stability of the DFE on $\mathbb{R}^3_+ \times [0, F_{W^*}]$.

■

The formula on $\mathcal{R}_{0,\mathrm{dengue},W} \leq 1$ shows that when introduction of *Wolbachia* is sustainable, i.e., $\mathcal{R}_{0,\mathrm{offsp},W} > 1$, the natural basic reproduction ratio is multiplied by 3 factors, less then one, to obtain the basic reproduction ratio for dengue with *Wolbachia* infected mosquitoes.
Experiments suggest that the life span of infected females is reduced by more than half [55] for wMelPop-CLa and by 0.9 for wMel [76, 76]. Another experiments [76] show that there is a reduction of virus in the saliva of infected female mosquito. This reduction is 4.2 % for dengue virus. Practically this means a reduction around 0.042 for β_{Wvh}. It is not clear what happens for β_{Whv}.
With these results, and the above laboratory data we can now study the impact of *Wolbachia* introduction in the disease dynamics. There are many estimations of $\mathcal{R}_0$ in dengue epidemics in the literature:

Newton and Reiter [58] 1.9

Koopman et al. [46] 1.3

Marques et al. [52] $1.6 - -2.5$

Favier et al.[16] $8 - -22.8$

Ferguson [26] $1.38 - -8.47$

Chowell [14] $2.0 - -2.4$

Massad et al. [53] $3.6 - -12.9$

In the worst case, we have $\mathcal{R}_{0,\text{dengue},U} = 22.8$, and hence we obtain $\mathcal{R}_{0,\text{dengue},W} \leq 0.95$ after the introduction of *w*Mel. Note that if we choose the second worseestimative, i.e., [53] then $\mathcal{R}_{0,\text{dengue},W} \approx 0.54$.

5 Some other models of infection by *Wolbachia* : multiscaling

In this section we will revisit the model (6) of section 3 and show that it contains the bistability results of [71].
A large number of models on insecticide population dynamics with *Wolbachia*, and most of them (if not all of them) exhibits bi-stability. Thus, if infected population reach some threshold level, infected mosquitoes should invade an uninfected population.
On the other hand Barton and Turelli [5] and Turelli [71] obtain bi-stability of infected and uninfected mosquitoes, and also the critical frequency with relative simple arguments.
The question we address in this section is how to systematically link the present model to these simpler results.

Most models assume, as we does, that *Wolbachia* infection has only two effects:

1. Cytoplasmic incompatibility: infected male with uninfected female produce a hatch rate $H < 1$ relative to the rate of the other possible crosses.
2. infected female has a relative fecundity rate $F < 1$.

In addition, we also assume that infected mosquitoes have their lifespan reduced by a factor of s_v.
Also we follow the notation in [5] and write,

$$s_h = 1 - H \quad \text{and} \quad s_f = 1 - F.$$

We shall x denote the frequency of infected adult mosquitoes.
Then, according to [5] , the critical frequency is given by

$$\hat{x} = \frac{s_f + s_v - s_f s_v}{s_h}.$$

We show now try to recover the result above from our model (6).
We shall write

$$L_* = \epsilon^{-b}\bar{L}_*, \quad E_* = \epsilon^{-a}\bar{E}_*, \qquad * = I, U.$$

We also write

$$\begin{aligned} \mu_E &= \epsilon^{a-b}\bar{\mu}_E, & \eta_E &= \epsilon^{a-b}\bar{\eta}_E, \\ \mu_2 &= \epsilon^{b}\bar{\mu}_2, & \mu_P &= \epsilon^{-b}\bar{\mu}_P, \\ \eta_P &= \epsilon^{-b}\bar{\eta}_P, & \beta &= \epsilon^{-b}\bar{\beta}, \\ \eta_Y &= \epsilon^{-b}\bar{\eta}_Y \end{aligned}$$

and

$$\mu_{FU} = \epsilon^{-b}\bar{\mu}_{FU}, \quad \mu_{FW} = \epsilon^{-b}\bar{\mu}_{FW},$$
$$\mu_{MU} = \epsilon^{-b}\bar{\mu}_{MU}, \quad \mu_{MW} = \epsilon^{-b}\bar{\mu}_{MW}, \quad \phi = \epsilon^{-b}\bar{\phi}.$$

Notice that, typically, we should have $a > b$ meaning that there are more eggs than larvae. In this case we find the following system:

$$\dot{\bar{E}}_U = \epsilon^{a-b}\left[\bar{\phi}\, F_{UU} - (\bar{\mu}_E + \bar{\eta}_E)\ \bar{E}_U\right]$$

$$\dot{\bar{L}}_U = \bar{\eta}_E\, \bar{E}_U - \left[\eta_L + \mu_L + \bar{\mu}_2\,(\bar{L}_U + \bar{L}_W)\,\right]\bar{L}_U$$

$$\epsilon^b \dot{P}_U = \eta_L\, \bar{L}_U - (\bar{\mu}_P + \bar{\eta}_P)\, P_U$$

$$\epsilon^b \dot{Y}_U = \nu\, \bar{\eta}_P\, P_U - (\bar{\beta} + \bar{\mu}_Y)\, Y_U$$

$$\epsilon^b \dot{F}_{UU} = \bar{\beta}\, Y_U\, \frac{M_U}{M_U + M_W} - \bar{\mu}_{FU}\, F_{UU}$$

$$\epsilon^b \dot{F}_{UW} = \bar{\beta}\, Y_U\, \frac{M_W}{M_U + M_W} - \bar{\mu}_{FU}\, F_{UW}$$

$$\epsilon^b \dot{M}_U = (1-\nu)\, \bar{\eta}_P\, P_U - \bar{\mu}_{MU}\, M_U \tag{17}$$

$$\epsilon^b \dot{\bar{E}}_W = \theta\, \bar{\phi}\,(F_{WW} + F_{WU}) - (\bar{\mu}_E + \bar{\eta}_E)\ \bar{E}_W$$

$$\dot{L}_W = \eta_E\, \bar{E}_W - \left[\eta_L + \mu_L + \bar{\mu}_2\,(\bar{L}_W + \bar{L}_U)\,\right]\bar{L}_W$$

$$\epsilon^b \dot{P}_W = \eta_L\, \bar{L}_W - (\bar{\mu}_P + \bar{\eta}_P)\, P_W$$

$$\epsilon^b \dot{Y}_W = \nu\, \bar{\eta}_P\, P_W - (\bar{\beta} + \bar{\mu}_Y)\, Y_W$$

$$\epsilon^b \dot{F}_{WU} = \bar{\beta}\, Y_W\, \frac{M_U}{M_U + M_W} - \bar{\mu}_{FW}\, F_{WU}$$

$$\epsilon^b \dot{F}_{WW} = \bar{\beta}\, Y_W\, \frac{M_W}{M_U + M_W} - \bar{\mu}_{FW}\, F_{WW}$$

$$\epsilon^b \dot{M}_W = (1-\nu)\, \bar{\eta}_P\, P_W - \bar{\mu}_{MW}\, M_W$$

Notice that the dynamics of the Eggs is on the slower time scale. We now introduce a slower time scale

$$t = \epsilon^{-(a-b)} T$$

We shall abuse language and write $\dot{F}$ for $\dfrac{dF}{dT}$, and we then obtain

$$
\begin{aligned}
\dot{\bar{E}}_U &= \left[\bar{\phi}\, F_{UU} - (\bar{\mu}_E + \bar{\eta}_E)\ \bar{E}_U\right] \\
\epsilon^{a-b}\dot{\bar{L}}_U &= \bar{\eta}_E\, \bar{E}_U - \left[\eta_L + \mu_L + \bar{\mu}_2\,(\bar{L}_U + \bar{L}_W)\right]\bar{L}_U \\
\epsilon^{a}\dot{P}_U &= \eta_L\, \bar{L}_U - (\bar{\mu}_P + \bar{\eta}_P)\, P_U \\
\epsilon^{a}\dot{Y}_U &= \nu\, \bar{\eta}_P\, P_U - (\bar{\beta} + \bar{\mu}_Y)\, Y_U \\
\epsilon^{a}\dot{F}_{UU} &= \bar{\beta}\, Y_U\, \frac{M_U}{M_U + M_W} - \bar{\mu}_{FU}\, F_{UU} \\
\epsilon^{a}\dot{F}_{UW} &= \bar{\beta}\, Y_U\, \frac{M_W}{M_U + M_W} - \bar{\mu}_{FU}\, F_{UW} \\
\epsilon^{a}\dot{M}_U &= (1-\nu)\, \bar{\eta}_P\, P_U - \bar{\mu}_{MU}\, M_U \\
\epsilon^{a}\dot{\bar{E}}_W &= \theta\, \bar{\phi}\,(F_{WW} + F_{WU}) - (\bar{\mu}_E + \bar{\eta}_E)\ \bar{E}_W \\
\epsilon^{a-b}\dot{\bar{L}}_W &= \eta_E\, \bar{E}_W - \left[\eta_L + \mu_L + \bar{\mu}_2\,(\bar{L}_W + \bar{L}_U)\right]\bar{L}_W \\
\epsilon^{a}\dot{P}_W &= \eta_L\, \bar{L}_W - (\bar{\mu}_P + \bar{\eta}_P)\, P_W \\
\epsilon^{a}\dot{Y}_W &= \nu\, \bar{\eta}_P\, P_W - (\bar{\beta} + \bar{\mu}_Y)\, Y_W \\
\epsilon^{a}\dot{F}_{WU} &= \bar{\beta}\, Y_W\, \frac{M_U}{M_U + M_W} - \bar{\mu}_{FW}\, F_{WU} \\
\epsilon^{a}\dot{F}_{WW} &= \bar{\beta}\, Y_W\, \frac{M_W}{M_U + M_W} - \bar{\mu}_{FW}\, F_{WW} \\
\epsilon^{a}\dot{M}_W &= (1-\nu)\, \bar{\eta}_P\, P_W - \bar{\mu}_{MW}\, M_W
\end{aligned}
\tag{18}
$$

We now use a slaving argument, to obtain the following relationships:

1. For the U variables we find:

$$
\begin{aligned}
&\bar{E}_U = \frac{1}{\bar{\eta}_E}\left[\eta_L + \mu_L + \bar{\mu}_2\left(\bar{L}_U + \bar{L}_W\right)\right]\bar{L}_U, \qquad \bar{L}_U = \frac{\bar{\mu}_P + \bar{\eta}_P}{\eta_L} P_U, \\
&P_U = \frac{\bar{\mu}_{MU}}{(1-\nu)\bar{\eta}_P} M_U
\end{aligned}
$$

and

$$Y_U = \frac{\nu\bar{\eta}_P}{\bar{\beta}+\bar{\mu}_Y}P_U, \quad F_{UU} = \frac{\bar{\beta}}{\bar{\mu}_{FU}}Y_U\frac{M_U}{M_U+M_W}$$

2. For the W variables we find:

$$\bar{E}_W = \frac{1}{\bar{\eta}_E}\left[\eta_L+\mu_L+\bar{\mu}_2\left(\bar{L}_U+\bar{L}_W\right)\right]\bar{L}_W, \quad \bar{L}_W = \frac{\bar{\mu}_P+\bar{\eta}_P}{\eta_L}P_W,$$
$$P_W = \frac{\bar{\mu}_{MW}}{(1-\nu)\bar{\eta}_P}M_W$$

and

$$Y_W = \frac{\nu\bar{\eta}_P}{\bar{\beta}+\bar{\mu}_Y}P_W, \qquad F_{WU} = \frac{\bar{\beta}}{\bar{\mu}_{FW}}Y_W\frac{M_U}{M_U+M_W},$$
$$F_{WW} = \frac{\bar{\beta}}{\bar{\mu}_{FW}}Y_W\frac{M_W}{M_U+M_W}$$

From this we get the following relationships

$$\frac{\bar{E}_U}{C_U} = \left[\eta_L+\mu_L+d_UM_U+d_WM_W\right]M_U$$
$$\frac{\bar{E}_W}{C_W} = \left[\eta_L+\mu_L+d_UM_U+d_WM_W\right]M_W$$
$$F_{UU} = \frac{\nu\bar{\beta}\bar{\mu}_{MU}}{(1-\nu)(\bar{\beta}+\bar{\mu}_Y)\bar{\mu}_{FU}}M_U\frac{M_U}{M_U+M_W}$$
$$F_{WU} = \frac{\nu\bar{\beta}\bar{\mu}_{MW}}{(1-\nu)(\bar{\beta}+\bar{\mu}_Y)\bar{\mu}_{FW}}M_W\frac{M_U}{M_U+M_W}$$
$$F_{WW} = \frac{\nu\bar{\beta}\bar{\mu}_{MW}}{(1-\nu)(\bar{\beta}+\bar{\mu}_Y)\bar{\mu}_{FW}}M_W\frac{M_W}{M_U+M_W}$$

where

$$C_U = \frac{(\bar{\mu}_P+\bar{\eta}_P)\nu\bar{\mu}_{MU}}{\bar{\eta}_E\eta_L(1-\nu)(\bar{\beta}+\bar{\mu}_Y)}, \quad C_W = \frac{(\bar{\mu}_P+\bar{\eta}_P)\nu\bar{\mu}_{MW}}{\bar{\eta}_E\eta_L(1-\nu)(\bar{\beta}+\bar{\mu}_Y)},$$

and

$$d_U = \frac{(\bar{\mu}_P+\bar{\eta}_P)\nu\bar{\mu}_{MU}\bar{\mu}_2}{\eta_L(1-\nu)(\bar{\beta}+\bar{\mu}_Y)}, \quad d_W = \frac{(\bar{\mu}_P+\bar{\eta}_P)\nu\bar{\mu}_{MW}\bar{\mu}_2}{\eta_L(1-\nu)(\bar{\beta}+\bar{\mu}_Y)}.$$

Let

$$Q_U = \frac{\bar{E}_U}{C_U} \quad \text{and} \quad Q_W = \frac{\bar{E}_W}{C_W}.$$

Write

$$r_U = \frac{\bar{\beta}\bar{\eta}_E\eta_L}{(\bar{\mu}_P+\bar{\eta}_P)\bar{\mu}_{FU}}, \quad r_W = \frac{\theta\bar{\beta}\bar{\eta}_E\eta_L}{(\bar{\mu}_P+\bar{\eta}_P)\bar{\mu}_{FW}}.$$

Then, system (18) can be reduced to

$$\begin{aligned}
\dot{Q_U} &= r_UM_U\frac{M_U}{M_U+M_W} - \left[\eta_L+\mu_L+d_UM_U+d_WM_W\right]M_U \\
\dot{Q_W} &= r_WM_W - \left[\eta_L+\mu_L+d_UM_U+d_WM_W\right]M_W \\
Q_U &= \left[\eta_L+\mu_L+d_UM_U+d_WM_W\right]M_U \\
Q_W &= \left[\eta_L+\mu_L+d_UM_U+d_WM_W\right]M_W
\end{aligned} \tag{19}$$

System (19) can be rewritten as a system for (M_U, M_W) but it turns out that this will not be necessarily in the subsequent analysis.

We can now link our results to those of Turelli [71]. We write

$$x = \frac{M_W}{M_U + M_W}$$

Notice that

$$\frac{M_W}{M_U + M_W} = \frac{Q_W}{Q_U + Q_W}.$$

Hence

$$\begin{aligned}
\dot{x} &= \frac{\dot{Q_W}}{Q_U + Q_W} - \frac{Q_W(\dot{Q_U} + \dot{Q_W})}{(Q_U + Q_W)^2} \\
&= \frac{1}{Q_U + Q_W}\left(\dot{Q_W}(1-x) - x\dot{Q_U}\right) \\
&= \frac{1}{\eta_L + \mu_L + d_U M_U + d_W M_W}\left(r_W x(1-x) - r_U x(1-x)^2\right) \\
&= \frac{1}{\eta_L + \mu_L + d_U M_U + d_W M_W} x(1-x)(r_W - r_U + r_U x)
\end{aligned}$$

The last system is topologically conjugated to

$$\dot{x} = x(1-x)\left(x - \frac{r_U - r_W}{r_U}\right).$$

which is bistable as expected, with the critical frequency given by the equilibrium point:

$$x^* = 1 - \frac{r_W}{r_U} = 1 - \theta\frac{\bar{\mu}_{FU}}{\bar{\mu}_{FW}} = 1 - \mathcal{R}_{0,W}$$

$$\hat{x} = x^*$$

we recover Turelli's critical frequency.

6 Simulation and numerical results

In this section we will use simulations to study the relevance of our model. More peculiarly we will see that our model can replicate, with excellent agreement, the *Wolbachia* introduction into wild Australian *Aedes aegypti* populations near Cairns in north-eastern Australia [40]. We also study some strategies for introducing *Wolbachia* and the nature of the coexistence equilibrium. We also look for robustness issues and sensitivity analysis.

6.1 Relevance of the model

A key factor in simulation of a model is the choice of parameters. Until now, experiments have been done in Australia [40] with *Wolbachia* and local *Aedes aegypti* populations. We will use the results of these experiments to identify some of the parameters in the present model. Some parameters might depend on the environment and the identification described in the following correspond to an experiment in Cairns [40] and to the introduction of *w*Mel *Wolbachia* strain.

The first field trials to test introduction of *w*Mel *Wolbachia* began in Cairns in January 2011 during the wet season. Mosquitoes were released once a week for 10 weeks from properties, in the two trial sites of Yorkeys Knob and Gordonvale. Yorkeys Knob (614 houses), is 15 km north of Cairns and Gordonvale (668 houses), 20 km south of Cairns. Both communities are geographically contained townships surrounded by cane fields, highway or ocean allowing to more easily monitor the spread of the *Wolbachia* into the wild mosquito population.
In the month before release, residential properties within the release area were visited and water was removed from visible breeding containers. This has consequences on the capacity of the environment and therefore also on the value of the parameters. Adult female and male mosquitoes were released in Yorkeys Knob and Gordonvale sites spread uniformly throughout each field location. Adult *A. aegypti* populations were monitored in the release area by BioGents Sentinel mosquito traps (BGS) which are an effective surveillance tool for female adult *A.* aegypti. Ovitraps were also deployed in the release zone. The infection frequencies of Larvae were observed and appear as thick horizontal black lines in figure S4 of the supplement [39]. The number of larvae per breeding site influences the availability of food; therefore, since larval density plays an indirect role in the regulation of development [28], then μ_2 is an important factor.
As observed by the authors of [40]

> several critical parameters, specifically population sizes and daily survival rates, are poorly known.

Depending on the literature the average life expectancy can vary from 4 days (e.g., [51]), 10 days [27] to 40 days [54]. We choose an intermediate value from [49] and start with a mean life of 16 days.
Now in our model, two parameters are driving the final size of the wild and infected populations : the recruitment rate given by ϕ and the intraspecific competition for larvae μ_2. These two parameters depends heavily on the environment.
Therefore, we use literature-range values for the parameters that are considered known, and adjust mu_2 such that our model yields the first observed frequency in Yorkeys Knob. At this point no adjustments using least square methods are done.
With the values of parameters given in Table 5 we obtain the following results

Table 2: Parameters definition and possible values for Yorkeys Knob

Symbol	Definition	Value	References
ϕ	Rate of eggs production	$4\ d^{-1}$	[49, 61, 70, 78]
μ_E	Death rate of Eggs	$0.0100503\,d^{-1}$	[49, 61, 70, 78]
η_E	Hatching time	$0.25\,d^{-1}$	[49, 61, 70, 78]
η_L	Transmission rate Larvae	$0.0833\ d^{-1}$	[4, 9, 28, 49, 67, 69, 70]
μ_L	Death rate Larvae	$0.10536\,d^{-1}$	[4, 9, 28, 49, 67, 69, 70]
μ_2	Intraspecific competition	0.000049	[4, 21, 49, 67]
μ_P	Death Rate Pupae	0.01005	[4, 9, 28, 49, 67, 69, 70]
η_P	Transmission rate Pupae	$0.5\ d^{-1}$	[4, 9, 28, 49, 67, 69, 70]
ν	Sex ratio	0.5	[28]
β	Transmission rate Y to F	0.2	[4, 9, 28, 49, 67, 69, 70]
μ_Y	Death rate young female	$0.0202\ d^{-1}$	[49]
μ_{FU}	Death rate uninfected female	$0.061\,d^{-1}$	[49]
θ	Infect.Reduction hatching time	1	[40, 55, 56, 78, 79]
μ_{FW}	Death rate female infected	$0.068\ d^{-1}$	[40, 55, 56, 78, 79, 76]
μ_{MW}	Death rate male infected	$0.068\ d^{-1}$	[40, 55, 56, 78, 79, 76]

The frequencies given by the model, in figure 1, are satisfactory.

With the same set of parameters, we can now look at different scenarios of introduction of infected mosquitoes and simulate the evolution of the infected females. As indicated in [40] the sex ratio of the releases was close to $1:1$. The authors also assume that a stable stage distribution for the uninfected population. Hence we start from the equilibrium computed in subsection 3.1.1, for the uninfected population, and we add half the first release to M_W and F_{WW}. Population at the other infected stages is set to zero. Then we simulate one week and then restart the model with a new initial condition which is the last value obtained, to which we add the second release. The experience was done for 10 releases and the frequencies computed for 17 weeks.

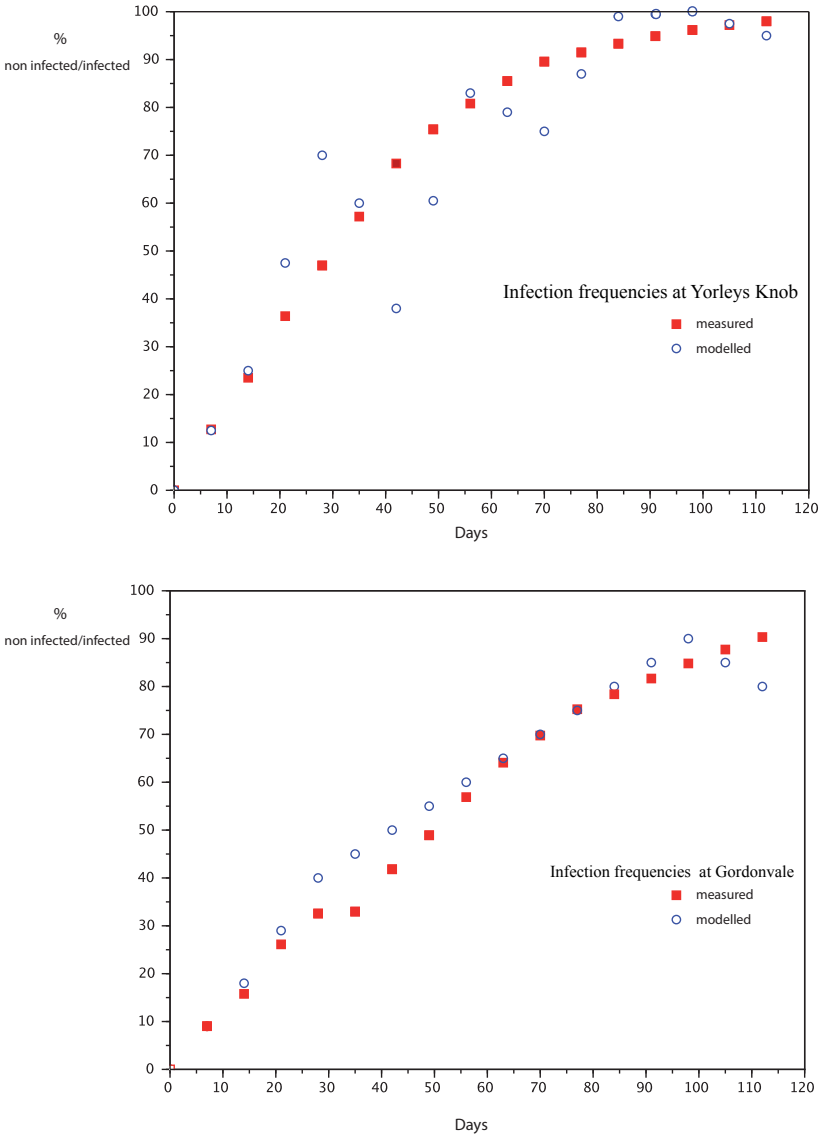

Figure 1: Frequencies observed and predicted. The red squares are the frequencies of infection given by the model. The blue circles are the frequencies observed in [40]

.

We can now simulate the experiments in Yorkeys Knob and Gordonvale using these identified parameters.

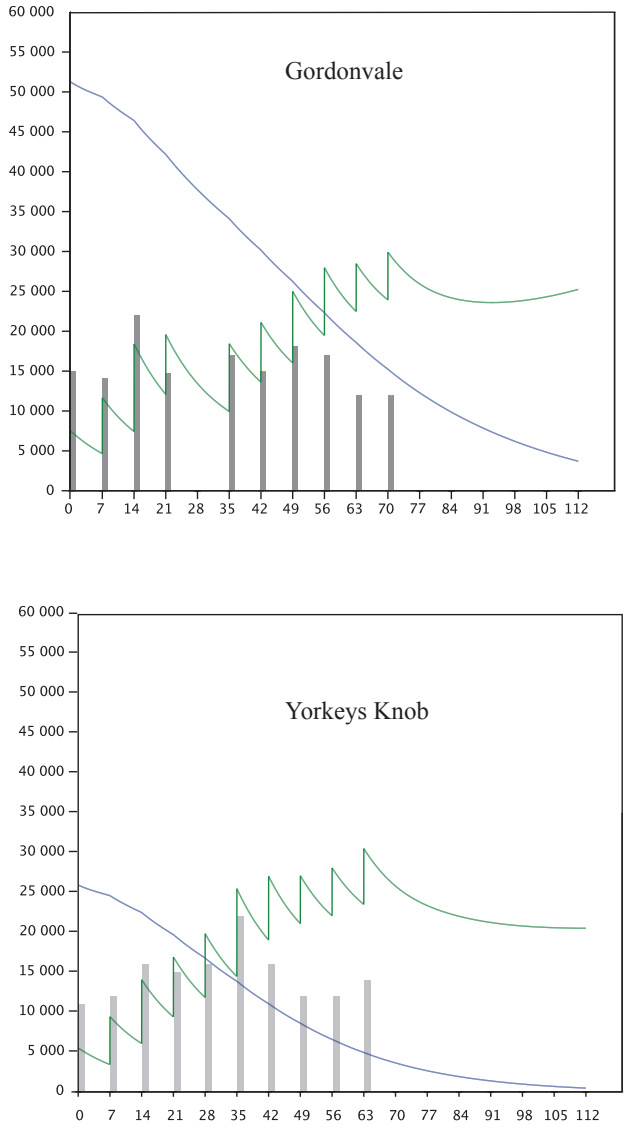

Figure 2: Curves of the uninfected in blue and infected female in green. The 10 releases are in grey

Tropical Cyclone Yasi landed on day 28 and disrupted *Wolbachia* monitoring collections at Yorkeys Knob. A planned release at Gordonvale on day 28 was cancelled and replaced by a release on week 11. As already observed, a release of mosquito is composed of nearly half females

and half males. In figure 3 we plot the complete release.

The only adjustment we made is that of μ_2, which amounts to simply setting the model relatively to the initial wild population,assumed to be at equilibrium. This depends on the environmental constants. Then, as a by product, we have a method to estimate the initial wild population. We estimate the number of females at 25900 for Yorkeys and at 51200 in Gordonvale. This corresponds to the observations of [40] : "the resident *A. aegypti* population in Gordonvale was roughly twice as large as in Yorkeys Knob. Both areas had comparable release sizes. Then we observe that in Yorkeys in day 63, after the last release, the population of infected females (F_{WW}) is over the uninfected free equilibria. On the other hand in Gordonvale the the population of infected females (F_{WW}) is increasing and will stabilize to the equilibria.

In a recent paper [63], a subset of the authors of [40], propose to estimate the initial population of *A. aegypti* in Yorkeys and Gordonvale using the field trial described above. They found 7862 in Yorkeys Knob and 7261 in Gordonvale.

This contradicts the claims of the same authors in [40]. They said " The resident *A. aegypti* population in Gordonvale was roughly twice as large as in Yorkeys Knob" and this is confirmed by the number of female : "Our BGS data indicate that Gordonvale has roughly twice as many females per premise as Yorkeys Knob" [40].

However in [63] the estimated number in Gordonvale is approximatively equal, but actually less than the number estimated in Yorkeys.

A reason for this underestimation is their use of a discrete model with a huge death rate. The authors use a survival of 0.75 in Yorkeys which corresponds to a death rate of 3.5, i.e., a mean life of 3.4 days ! This value can be encountered in the literature, but in this case gives contradictory results. In Gordonvale they estimate the death rate to be 0.105 in other words a mean life of 9.4 days.

The frequencies of infected larvae was also monitored. Figure S4 of [39] shows the observed infection frequencies in each suburb. We compare the larval frequencies observed in [39] with the ones that given by our model in figure 3. The observation was done each two weeks, from weak 3 to weak 15.

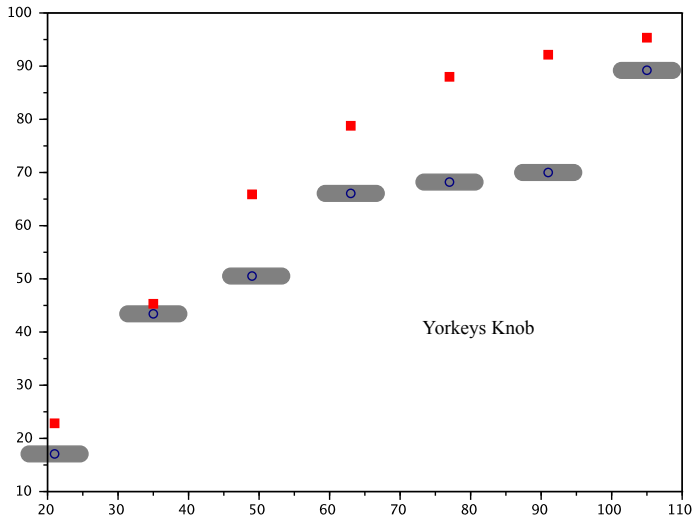

Figure 3: Observed larval infection frequencies in grey (as in [39]) and square red for our model

Our model overestimates the frequencies of the larval infection. One reason, as invoked also by the authors of [40] can be "The faster rise of the infection frequency and the unexpected dips make these data harder to fit ... ".

However the predictions we obtained are coherent and are relatively good for the end of the trial.

6.2 Numerical explorations

6.2.1 Continuation in Gordonvale

The CWIE in Gordonvale is, according to our model

```
CWIE=(792066.61,   76347.302,    12473.32,    14161.18,    41195.86,    45357.198 )
```

As seen in the figure 3 on day 120 the population of F_{WW} is `25 239`, far from the equilibria, even if the frequency of infected female is 95%. But in this frequency we incorporate the number of female F_{WU} which will tends to zero. If we extend the solution in Gordonvale we obtain

Table 3: Continuation of Gordonvale after day 120

Day after 120	$\frac{F_{WW}}{F_{WW}+F_{WU}}$	% F_{WW} from the CWIE
30	96 %	75 %
50	99.04%	84%
100	99.95%	95.87%
200	99.99%	99.6%

6.2.2 Release strategy in Gordonvale

The strategy of releases chosen in Gordonvale was efficient and arrive in the attraction basin of the CWIE. However roughly the same number of mosquitoes were released in Gordonvale and Yorkeys, around 150 000. We try some numerical experiments and look at the results for each experience after week 16 :

- a unique release of `150 000` at the beginning,

- releasing with the same schedule as the real trial, but doubling the amount of mosquitoes and limiting to 5 weeks. For comparison reasons, we do not release during the hurricane event.

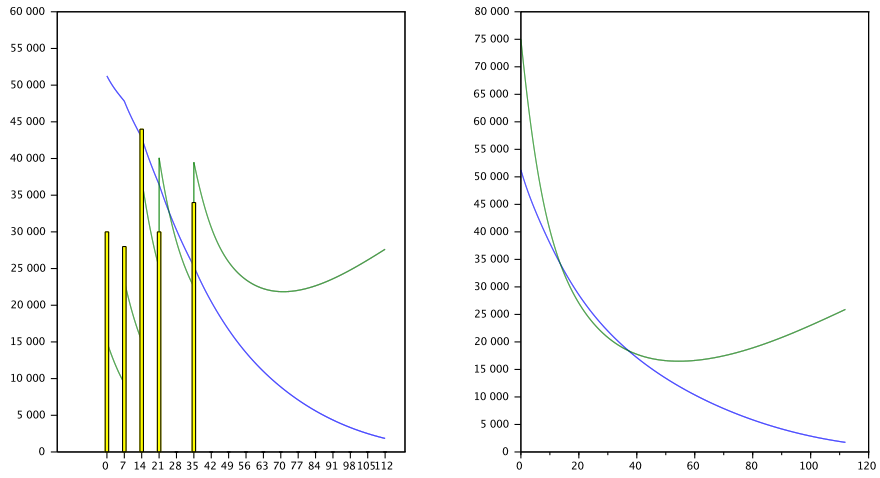

Figure 4: simulations Gordonvale : on the left five releases, on the right one release of 150 000. In blue the curve of uninfected females.

The results are presented in figure 4. The efficiency at day 112 is given by the following table

Table 4: Comparison of efficiency. Percentages given at day 112.

Release	$\frac{F_{WW}}{F_{WW}+F_{WU}}$	% F_{WW} from the CWIE
150 000 in one release	93.69%	62%
5 releases	93.79%	67%
Trial release	87%	61%

From this preliminary “in silico" experiments we can conclude that to establish successfully *Wolbachia*, we have to answer to the questions “how much” and “when and how"

How much The number of mosquitoes released depends heavily on the initial size of the wild population. Our model can help to predict the necessary amount of mosquitoes to be released, after the first measurement following the first release.

When and how It seems that releasing more mosquitoes at the beginning is better, fragmented releases seems also more efficient. However there is certainly a limitation in the feasible production of infected mosquitoes and probably also limitations on the environment carrying capacity.

These results should be further confirmed by validation with data from other experimental trials.

6.3 The coexistence equilibrium

We can compute the coexistence equilibrium and the eigenvalues of the Jacobian computed at this equilibrium. We obtain the following values

```
- 3.9610977
- 2.0745037
- 0.5637610
- 0.5367267
- 0.2471946 + 0.1702506i
- 0.2471946 - 0.1702506i
- 0.2474402 + 0.1238719i
- 0.2474402 - 0.1238719i
  0.0036353
- 0.0213270
- 0.0660850
- 0.0687505
- 0.0687505
```

This result confirms that the coexistence equilibrium is unstable. A new result appears, with sensible biological parameters, the stable manifold is of codimension one. We also observe that since the positive eigenvalue is `0.0036353`, i.e., the stable manifold is slowly repulsive. This means, from a practical point of view, that any strategy must avoid the vicinity of the coexistence equilibrium.
The coexistence equilibrium (Yorkeys) is given by

```
[ 28 4378, 34 264, 5597, 6355, 18488, 22617,35108, 4230, 691, 784, 2054, 228, 2513 ]
```

With this result, it is clear that releasing 5000 infected males and 5000 infected females from the DFE gives an initial point which is driven away from the coexistence equilibrium. This confirms the validity of the strategy used.

6.4 *Wolbachia* and Dengue

We choose, for the mosquito population, the parameters of Yorkeys Knob. The others parameters are given in the following table :

Table 5: Parameters definition and possible values for Yorkeys Knob

Symbol	Definition	Value and References
Λ	Recruitment rate for the human population	
β_{Wvh}	Transmission coefficient from infected mosquito	0.042*β_{Uvh} [76]
β_{Uvh}	Transmission coefficient from uninfected mosquito	`0.17789` [54]
μ_h	Human death rate	Austral. B. Stat. `0.000034`
γ_h	Incubation of Dengue	`1/7` CDC and WHO
δ_h	Duration of viremia	`1/5` CDC and WHO
$beta_{Whv}$	Transmission to infected mosquito	`0.17789` [54]
β_{Uhv}	Transmission to uninfected mosquito	`0.17789` [54]

We make pessimistic assumptions on the transmissions rates, i.e., $\beta_{Uvh} = \beta_{Whv} = \beta_{Uhv}$. The parameter Λ is set to give a population corresponding to Yorkeys Knob, i.e., 2700 individuals. The duration of viremia and time to recover from dengue are classical. With these parameters we obtain

$$\mathcal{R}_{0,\text{dengue},U} = 24.519443 \ ; \quad \mathcal{R}_{0,\text{dengue},W} = 0.74714$$

Note that $\mathcal{R}_{0,\text{dengue},U}$ is greater than the worst value founded in the literature (see section 4). We will consider four scenarios for the in-silico experiments:

1. 20 infectious individuals are introduced in the population and the population of mosquitoes is entirely composed of uninfected mosquitoes at the equilibrium.

2. After the introduction of infected mosquitoes, corresponding to the release in Yorkeys Knob we introduce at the beginning of the week 17, 20 infected humans with dengue.

3. After the introduction of infected mosquitoes, corresponding to the release in Yorkeys Knob we introduce at the beginning of the week 20, 20 infected humans with dengue.

4. After the introduction of infected mosquitoes, corresponding to the release in Yorkeys Knob we introduce at the beginning of the week 30, 20 infected humans with dengue.

In the first case an epidemic with a peak of `652` infected individual appears. In the second case, even with remaining uninfected mosquitoes, there is no a real epidemic and dengue tends to disappear, but very slowly. We plot the different simulations in figure 5.

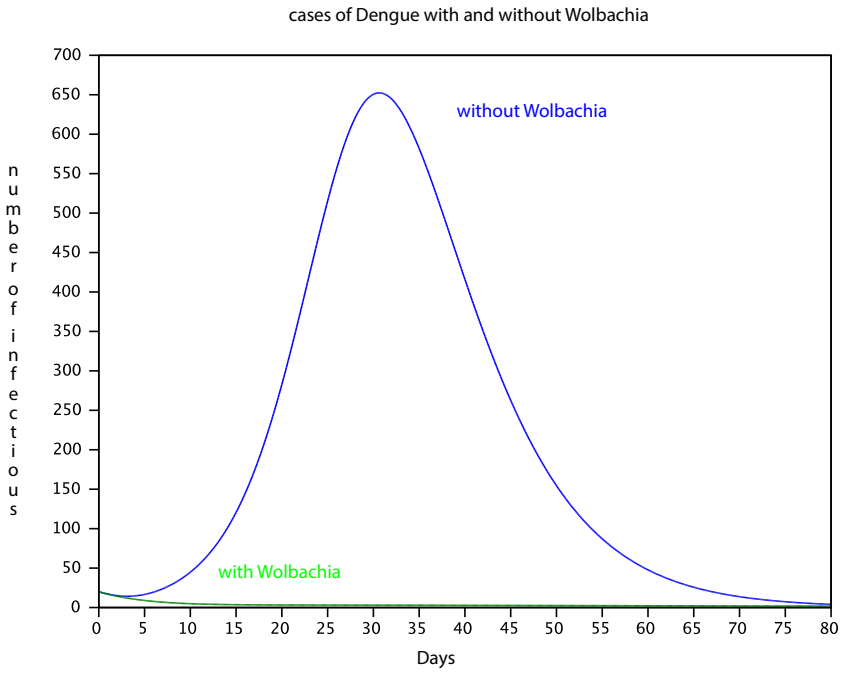

Figure 5: In green the infected human with *Wolbachia* presents. In blue without infected mosquitoes

It can seems strange that without *Wolbachia* dengue seems to disappears. This is a due to the scale chosen. Actually with $\mathcal{R}_{0,\text{dengue},U} = 24.519443$, the system converge to an endemic equilibrium, but with the values of our parameters the value of I_h, at this equilibrium, is very small (namely `0.43`). However all the population is quasi immunized.

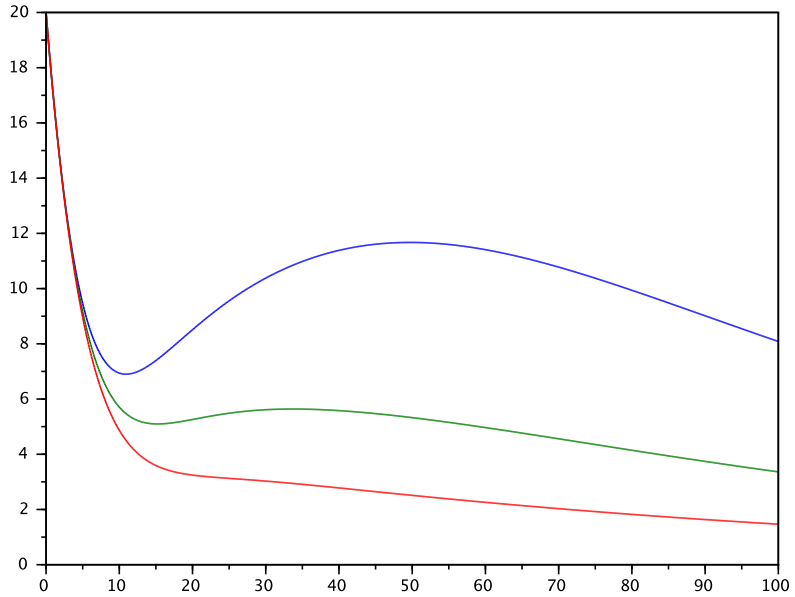

Figure 6: Curves of the infectious individuals. In blue dengue after week 17, in green after week 20, in red after week 30.

If dengue appears 20 weeks after the start of the releases, the situation is better and finally after 30 weeks no epidemic occurs. In figure 6, we plot a zoom on the three situations. The difference is simply the residual of *Wolbachia* uninfected mosquitoes in each situation. There is a small rebound due to the infections caused by the uninfected mosquitoes for the two first simulations.

6.5 Robustness and sensitivity analysis issues

We will in this section address the issue of the robustness of the stability of the CWIE, is crucial for our results. Robustness will be evaluated by estimating the distance, for a matrix norm, of the stable Jacobian computed at the CWIE. The stability of the CWIE has been obtained in section 3.3.2 and depends only on the stability of the matrices A_{11} and A_{22}. Usually computing the distance from a Hurwitz matrix to the nearest unstable matrix is a difficult optimization problem. This problem has been solved in 1988 [13], where an algorithm has been proposed. However this distance has been computed for complex perturbations and the algorithm compute the so-called complex stability radius.

$$r_{\mathbb{C}}(A) = \inf_{\substack{s(A+\Delta)\geq 0 \\ \Delta\in\mathbb{C}^n}} \| \Delta\|_2$$

This stability radius is linked to pseudo spectra. If the perturbations are real then the problem is presently not completely solved. For general matrices with structured perturbations, or for nonnegative perturbations the problem is still open. Nevertheless our matrices are not completely general and A_{11} and A_{22} are Metzler matrices regardless of the perturbations on the

parameters. Furthermore the perturbations, that we have to consider, are structured, i.e., only the nonnegative entries of this matrices are modified. For Metzler matrices the problem has been solved partially in [66] where for structured perturbations the stability radius is computed. More precisely for a A a Hurwitz Metzler real matrix, we consider perturbations of A of the type $A + D\,\Delta\,E$, where D and E are nonnegative given matrices and Δ is the perturbation. Stability radius $r(A, D, E)$ (respectively real, complex, or nonnegative) can be defined, as before, depending on Δ which is respectively real, complex or nonnegative. The result is (theorem 5, [66]), that for any subordinated monotonic norm

$$r_{\mathbb{C}}(A, D, E) = r_{\mathbb{R}}(A, D, E) = r_{\mathbb{R}_+}(A, D, E)) = \frac{1}{\|E\,A^{-1}\,D\|}$$

We can now examine the distance to instability of A_{11} and A_{22} given in section 3.3.2. Actually whatever are the admissible real perturbations on A_{11} (i.e., which let A_{11} Metzler) the spectrum of A_{11} is given by its diagonal. Then for the Frobenius norm the distance to instability for such perturbations is

$$r_{A_{11}\in\mathcal{M}}(A_{11}) = \min\left(\mu_E + \eta_E, (\beta + \mu_Y)\,(\mu_L + \eta_L)\,\mathcal{R}_{0,\text{offsp},W}, (\mu_P + \eta_P), (\beta + \mu_Y), \mu_{FU}, \mu_{MU}\right),$$

where $\mathcal{M}$ denotes the set of Metzler matrices.
The case of A_{22} is more complex. However the stability of A_{22} is completely equivalent to the stability of the matrix introduced $D - C\,A^{-1}\,B$ introduced in section 3.3.2. It is immediate that the distance, e.g., for the Frobenius norm is then

$$r_{A_{22}\in\mathcal{M}} = \min\left(\mu_{FW}, \mu_{FW}\,\frac{(\mathcal{R}_{0,\text{offsp},W} - 1)}{(2\,\mathcal{R}_{0,\text{offsp},W} - 1)}\right).$$

For example for the set of parameters corresponding to Yorkeys Knob in table 5, the stability radius of the Jacobian is

$$r_{J(CWIE)\in\mathcal{M}} \;=\; 0.06875.$$

This minimum is given by $\mu_{FW}\,\dfrac{(\mathcal{R}_{0,\text{offsp},W} - 1)}{(2\,\mathcal{R}_{0,\text{offsp},W} - 1)}$. But as $\mathcal{R}_{0,\text{offsp},W} > 1$ this radius will be positive. We are now ready to look at the robustness of $R_{0,\text{offsp},W} > 1$. Recall that this situation is linked to $\mathcal{R}_{0,W}$. We consider that we are in an environment where a population of *Aedes aegypti* is well established. Then the robustness question is linked to $\theta\,\dfrac{\mu_{FU}}{\mu_{FW}}$. Usually the basic offspring number for wild mosquitoes is high $R_{0,\text{offsp},U}$ is high. For example for Yorkeys Knob we obtained a number of 12.21 and for Gordonvale of 15.27. this means that for Yorkeys Knob we can allow a $\mathcal{R}_{0,W}$ of 0.082. In other words a reduction of hatching with an increase of death rate for the infected mosquitoes must be over a combined reduction factor of 0.082. Regarding the available data this situation is highly improbable [40, 76].
The situation for *w*MelPop-CLA is different. The increasing in death rate is multiplied roughly by 2 and fecundity declined at an accelerated rate which gives an estimated mean number for θ of 0.1-0.5 [8, 56, 72, 76, 79]. From the estimated number in the literature, the sustainability of the strain *w*MelPop-CLA is on the boundary of instability : 0.05-0.25. This will depends heavily of the value ecological factors (humidity, temperature ...). Our model is not adapted for such boundaries conditions. The same model can be used but with variations in the parameters. Robustness of *w*Mel is clear, but robustness of *w*MelPop-CLA must be considered more closely, particularly with data obtained from releases in the field.

7 Discussion

We have presented a model for studying the infection of *Wolbachia* in a population of *Aedes aegypti* mosquito. This model was designed for taking into account the measures obtained in the field. Using the data of the trial in Cairns [39, 40] our model behave remarkably well, both for the observed frequencies in adult females than the observed frequencies of larvae. However there is a need to confirm this behavior with data of other trials.
We propose a simple adjustment of the model parameters. This works for Gordonvale and Yorkeys Knob. Again this has to be confirmed with another experiments. The problem of the daily survival of female is critical and depends heavily of the local and time environment. As a by-product we can also estimate the initial population of vectors.
We also give some “in silico" experiments. We propose some preliminary conclusions. More analysis and simulations are needed and will appears elsewhere. A trade-off between the number of mosquitoes released and the production of infected mosquitoes has to be established. It seems that the more and the earlier is the better and that the size of the release has to be designed from the initial wild population of mosquitoes. Our findings indicates that the measures from BGS traps one week after the first release can be used to taylor the following releases. This strategy can also be pursued and the size of the next release can be computed from the preceding measures. In over words our model can be used to feedback the releases.
From our findings the release of *Wolbachia* is useful as preventive action against dengue. But the efficiency will depends on the frequency of the *Wolbachia* infected mosquitoes in the total population. This frequency must be sufficiently high and there is a delay to reach this situation. Again different scenarios must be experimented. This can be done with the parameters tuned for the local environment and depends on the entomological data available. The introduction of *Wolbachia* during a dengue epidemic is more delicate. It can be simulated but this is a sensitive issue.
We stress the fact that we work with the introduction of the strain *w*Mel of *Wolbachia*. To consider the strain *w*MelPop-CLA would necessitate detailed data and would probably does not so clear cut results.

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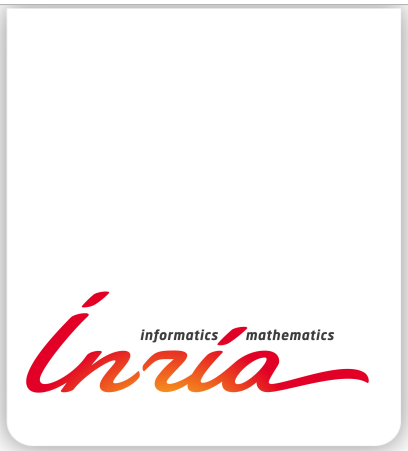

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